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Research Article

THE SYSTEMIC TOXIC RESPONSES OF PATIENTS TO TREATMENT WITH STREPTOKINASE STREPTODORNASE (SK–SD) [1, 2]

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This paper reports the results of investigations concerning possible toxicities associated with the therapeutic use of streptococcal concentrates containing streptokinase (SK) and streptodornase (SD).

Up to the present time the most obvious clinical side effect has been a pyrogenic reaction with associated symptoms of malaise, headache, arthralgia and occasionally nausea (1, 2). This reaction has been observed to begin about four to six hours after the local instillation of solutions of SK–SD; to reach its peak in 24 hours and to subside in the ensuing 24–48 hours. The febrile response occurs in 60–75% of the treated cases, with a suggestive higher frequency in patients with massive hemorrhage (hemothorax) than in those who have local suppurative disease of infectious origin. In patients receiving repeated injections the occurrence of the reaction has been unpredictable; sometimes appearing after the first injection and not subsequent ones and, on other occasions, after one or another of the later injections, but absent at the first treatment. Furthermore, the cause of the reaction has not yet been clearly determined but may be referable primarily either to the foreign materials of the solutions of SK–SD or to the breakdown products of their enzymatic action.

The present study was undertaken to determine whether untoward effects, inapparent to general clinical examination but that might be brought out by detailed laboratory examination, followed the use of SK–SD.

In addition to the routine need for such a study when a new agent is used therapeutically, there is a special need in the instance of SK–SD since disease is known to be associated with the presence of streptococci and their metabolic products within the body. It is useful, then, to look for laboratory changes that might indicate alterations suggestive of the specific toxicities of streptococcal products.

MATERIALS AND METHODS

Twenty-eight patients were studied, who received a total of 90 local instillations of SK–SD for a variety of suppurative and hemorrhagic diseases. Observations were made on the days before treatment; immediately prior to treatment; every one to three hours in the 12 hours after treatment; and then twice daily until control levels were obtained. In 10 patients, additional observations for possible delayed effects were made from 21 to 112 days after the last treatment.

Urinalysis was performed on each voided specimen on the day of treatment and thereafter until control observations were duplicated. The first 15 patients studied had complete routine analyses on each voided specimen, but the last 13 patients had each specimen routinely analyzed only during the first 12 hours after treatment, unless some change was observed during this period. Since we wished to determine the time relationship between the appearance of formed elements in the urine and clinical and peripheral blood changes, the urine was not pooled for the usual Addis counts during the first 24 to 48 hours following treatments. Instead, a 10 cc. sample of each voided specimen was centrifuged, 9 cc. of supernatant fluid discarded and the sediment resuspended in the residual 1 cc. The formed elements are, therefore, recorded as concentrations in each voided specimen.

Red blood cell and hemoglobin concentrations were determined by chamber counting and the Sahli acid hematin method. Two to four counts were done in the first 12–24 hours following treatments in the first 12 patients studied. Subsequently, a single count was done within 12 hours after treatment and then two or more in the following four days.

White blood cell and differential counts were performed in the usual manner. Two to four counts were done in the first 12 hours after therapy and then twice daily until control values were observed.

Erythrocyte sedimentation rate was measured by Westergren's method. Samples were taken once or twice

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[2] Supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

in the 12 hours after therapy and then at varying intervals of days following completion of a course of treatments.

Clotting times were done by a modification of the Lee-White method at 37° C. Determinations were made at the same intervals as the sedimentation rates. Subsequently, the clotted blood was incubated for 48–72 hours to determine stability of the clot.

Cephalin flocculation tests, using "DIFCO" cephalin-cholesterol, were performed at the same intervals as the erythrocyte sedimentation rates.

Clinical responses were evaluated in each patient. Temperature, pulse and respiration rates were determined every hour for three to six hours after therapy and then every four hours for the rest of the period of observation.

RESULTS

The following data are summarized in Figure 1.

Urinary findings: In 11 instances an increase in the concentration of white or red blood cells was observed in the absence of fever. In all other instances the urine changes coincided with a febrile reaction. All of the changes were transitory, having their onset less than 12 hours after therapy and subsiding in 24 to 48 hours.

RBC's were recorded as increased if one or more cells per cu. mm. in excess of control levels was noted. The average increase was 5 RBC/cu. mm. and the range from 1 to 40 RBC/cu. mm. In four of the 11 observed increases, only a single voided specimen showed change. In no case did the increase persist beyond 12 hours.

WBC's were recorded as increased if 10 or more cells per cu. mm. in excess of control levels were noted. The average increase was 300 WBC/cu. mm. and the range from 10 to 1,800 WBC/cu. mm. In eight of the 13 observed increases there was a coincident fever. The concentration of WBC's in the urine was not closely correlated with the peripheral blood leukocyte count. In six of the patients there was microscopic pyuria with each of 11 treatments; whereas, in the other two patients it was present on the first but not on subsequent treatments.

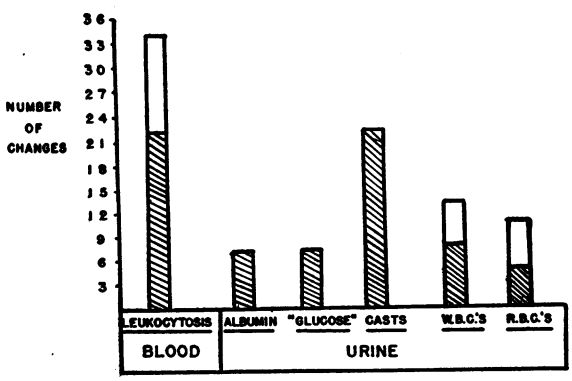

FIG. 1. SIGNIFICANT VARIATIONS OBSERVED IN BLOOD AND URINE, FOLLOWING LOCAL INSTILLATION OF SK–SD ON 90 OCCASIONS

The shaded areas represent association with fever; the unshaded areas represent changes occurring in the absence of fever.

Albumin and "glucose" estimations were made by the usual qualitative methods. Both albumin and "glucose" were coincidentally present in trace to 2 "plus" amounts on seven occasions. These reactions always coincided and occurred only with fever, usually appearing in only one or two voided specimens near the onset of the febrile response.

Casts appeared as a constant accompaniment of the febrile reaction, but not otherwise. Only hyaline casts were seen and they varied from 2 to 6/cu. mm.

Peripheral blood findings: The only significant change observed in the peripheral blood was a leukocytosis. An increase of 2,000 WBC/cu. mm. that was consistently exceeded in the next 12 hours by at least 2,000 WBC/cu. mm., was taken to mark the onset of leukocytosis. The average initial rise was 3,000 WBC/cu. mm.; the average maximum increase was 8,100 WBC/cu. mm. with a range of 3,000 to 18,000 WBC/cu. mm. above control levels. The onset of leukocytosis was frequently preceded by an initial fall in WBC during the first three hours following therapy. The onset of leukocytosis occurred within five hours after therapy and reached a maximum level in 12 to 24 hours. The control levels of the leukocyte count were observed in 24 to 48 hours from the onset of leukocytosis.

Eighteen of the 28 patients studied showed a leukocytosis following 34 of the 59 treatments they received. In no instance was a febrile reaction observed without a coincident leukocytosis; although in 12 instances a leukocytosis was observed in the absence of fever (Figure 1), comparable in degree to that seen associated with fever.

Differential counts demonstrated an increased percentage of metamyelocytes that paralleled the degree of leukocytosis, varying from 5% to 30% of the total number of leukocytes. In none of the

blood films were myelocytes or immature red blood elements observed that might suggest a response to hemolysis. There was no apparent alteration in the concentration or appearance of the blood platelets.

RBC counts and hemoglobin concentration remained unchanged.

Erythrocyte sedimentation rates showed no changes that appeared directly related to enzyme action. None of the rates showed a significant immediate decrease during therapy that would suggest intravascular fibrinogenolysis. Several patients' rates fell gradually after therapy as their clinical states improved. Ten patients were followed for 21 to 112 days after stopping enzyme therapy and none had sedimentation rates above the initial control levels.

Prothrombin times and clotting times did not change in relation to therapy; either as an early response during the first six hours after treatment or as a late effect after 24 to 72 hours. Clots incubated at 37° C. for 48–72 hours showed no evidence of lysis.

Cephalin flocculation tests were unchanged in 20 of the 23 patients examined. One of the three remaining patients had multiple fistulas from obstructive biliary tract disease and showed variable flocculation unrelated to therapy. A second patient had two control tests which showed 3 + flocculation after 48 hours. During the ensuing week he had three instillations of SK–SD into a shoulder joint and three tests taken during this week showed 1 +, 0 and ± flocculation after 48 hours. In the following week the flocculation was 2 +. A third patient had a negative control, but three days after treatment showed a 2 + flocculation and a return to negative at the time of the next examination on the tenth day.

Clinical response: Eleven patients had febrile reactions on 22 occasions during 35 treatments. The onset of fever occurred within four to six hours, the maximum level was reached within 24 hours of treatment and control levels were observed from 24 to 48 hours or less from the onset. The average initial rise was 2.2° F.; the average maximum level was 3.6° F. with a range from 1.8° F. to 7.0° F. The maximum rise was in a patient with hematothorax whose temperature rose from 98.2° to 105.2°. In a few instances the fever was preceded by a frank chill, but more commonly by chilly sensations. Since many of the patients had underlying disease that caused fever, the exact time relationship of the febrile response to the enzyme therapy was frequently difficult to determine.

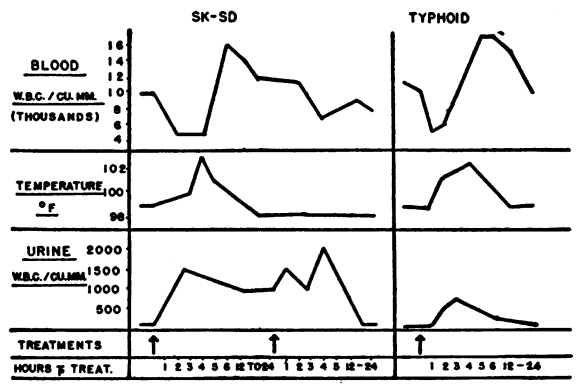

FIG. 2. OBSERVATIONS IN TWO PATIENTS

The first patient was treated on two successive days by intrapleural instillation of SK–SD. The second patient was given a single intravenous injection of triple typhoid vaccine.

Other than the changes in clinical findings classically associated with fever, there was no untoward change observed in the clinical state following therapy.

DISCUSSION

In evaluating the results, three factors had to be given consideration. First, an evaluation had to be made of the role that the disease for which the patient was being treated might have in producing changes in our observations. A control period of observation prior to therapy aided in evaluating this role, but actually we had no way of defining it accurately.

Second, the possibility of a foreign protein or pyrogen type of reaction—unrelated to the origin or mode of activity of the enzymes, but possibly related to the end products of their action—had to be considered. Here it was possible to compare the type of reaction that occurred after administration of SK–SD and an entirely dissimilar material to judge the degree of parallelism. In Figure 2 is charted the response of a patient who received two intrapleural injections of SK–SD on successive days, and a second patient who received a single IV injection of triple typhoid vaccine. The similarity of the reactions during the first 24 hours in these two diverse situations suggests that the

pattern of reaction is not a specific response to SK–SD. In the SK–SD treated patient the response to the second treatment illustrates the marked and erratic variation of response to SK–SD that was observed throughout the study. It was uncommon to observe simultaneous blood, temperature and urinary changes in response to SK–SD therapy, most of the patients showing changes in only one or two of these in response to a given treatment.

The third possibility considered was a direct toxicity of SK–SD itself. In choosing the methods of study, emphasis was given to measurements that might reflect changes observed acutely and chronically following streptococcal infection. The results demonstrated no chronic or delayed effects from SK–SD therapy. No acute effects were observed that could be considered characteristic of streptococcal disease. Further investigation of the dynamics of the febrile reaction is required.

SUMMARY AND CONCLUSIONS

1. Twenty-eight patients receiving 90 treatments with SK–SD were observed for evidence of acute and delayed toxicity.

2. Twenty of the patients had some type of reaction lasting from 12 to 48 hours after 44 of the 67 treatments they received.

3. The reactions consisted of 22 febrile responses to enzyme therapy, always associated with leukocytosis and the appearance of formed elements in the urine, and variably with "glycosuria" and proteinuria; as well as 22 occasions when leukocytosis or increased urinary red or white cells were observed in the absence of fever.

4. No delayed toxicity was observed.

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