

EFFECTS OF THE INTRAMUSCULAR ADMINISTRATION OF BAL (2,3 DIMERCAPTOPROPANOL) IN A SUBJECT WITH THE SICKLE CELL TRAIT: CASE REPORT

By WILLIAM J. KUHN, M.D.

A VARIETY of studies have indicated that the sickling phenomenon can be accelerated by a number of substances, when any one of the latter is mixed with the appropriate blood; these include carbon dioxide,¹ bacterial cultures,² sulfhydryl compounds such as H₂S, BAL (2,3 dimercaptopropanol), cysteine and glutathione,³ sodium bisulfite and cevitamic acid.⁴ However, there is no clear evidence that individuals harboring the sickle cell trait have ever developed sickle cell anemia, either spontaneously, or when exposed to agents which are known to accelerate sickling in vitro.

The sickle cell trait occurs in about 8 per cent of all Negroes in this country and is generally considered to be distinct from sickle cell anemia. The latter occurs in a much smaller proportion of the Negro population. The former condition is recognizable by observing the development of sickling in moist sealed preparations of freshly drawn blood. Sickle cell anemia is, in addition, associated with a variety of clinical manifestations: anemia, signs of increased blood destruction, abdominal pain, and other diverse effects, most of them related to an increased tendency to circulatory stasis and thrombosis.

The case to be described is one in which acceleration of sickling occurred in an individual harboring the sickle cell trait who was given BAL in oil intramuscularly. Exposure to this known accelerating compound failed to precipitate the picture of sickle cell anemia.

CASE REPORT

The patient was a Negro female who entered another hospital on July 9, 1948, with complaints of sore throat, fever, headache and rash. The serologic test for syphilis was found to be strongly positive and she was therefore given penicillin and arsenic treatment for six days. Following this she was transferred to the Salt Lake General Hospital where intensive antiluetic treatment with penicillin, mapharsen and bismuth was initiated. On the seventh day of treatment, she became disoriented and generally uncooperative. Because she was thought to have developed an arsenical encephalopathy with psychosis, arsenic was discontinued and the patient was given BAL (2,3 dimercaptopropanol), 100 mg. in oil intramuscularly every four hours. At this time her temperature ranged from 102 to 103 F. The volume of packed red cells was 51 ml. per 100 ml., reticulocytes were 0.5 per cent, the van den Bergh 1.2 mg. per cent (indirect r.1), and the sedimentation rate 3.

In the ensuing ten days she received a total of almost 5 grams of BAL. Shortly after BAL was discontinued the volume of packed red cells was found to be 34 ml. and the reticulocyte count was normal. Thrombophlebitis developed at this time and, in addition, a consolidative process appeared in the lower part of the left lung which was compatible with a pulmonary infarct. The superficial femoral veins were ligated bilaterally. Her mental status remained poor. Serial lumbar punctures showed increases in spinal fluid protein up to 70 mg. per cent. The plasma iron was 48 micrograms per 100 ml.

From the Department of Medicine, University of Utah, College of Medicine, and the Salt Lake County General Hospital, Salt Lake City, Utah.

Ten days after the administration of BAL the reticulocyte count had increased to 10.4 per cent, the sedimentation rate was 35 ml. and the volume of packed red cells 23 ml. Repeated van den Bergh tests and icteric indices remained the same as on the original examination. Clinically the patient showed no evidence of jaundice. White blood counts showed increases up to 20,000 and a shift to the left with a slight myelocytic and myeloblastic response. The differential smear showed red cells which were slightly macrocytic, and the blood indices were confirmatory. An ascending urinary tract infection developed which was associated with numerous leukocytes in the urine, casts, elevated temperature and BUN, and cultures which were positive for coliform organisms. This was treated successfully with sulfadiazine over the next four weeks. Her impaired mental status persisted, as did her anemia. The pulmonary process and thrombophlebitis showed gradual improvement. Reticulocyte counts increased to as high as 13 per cent, following which they returned to normal. Urine and fecal urobilinogens yielded consistently normal values. Several previous twenty-four hour sickling preparations had all been negative. However, it was later found that sickling preparations which stood for more than twenty-four hours yielded positive findings and it may be assumed that these would have been positive earlier had sufficient time been allowed. In view of the fact that sulphydryl compounds are known to accelerate sickling in vitro,³ it was thought that the use of BAL in this patient may have produced an acceleration of sickling in vivo, with subsequent thrombotic phenomena and anemia.

TABLE 1.—*Influence of BAL on Rate of Sickling*

Date of Specimen	Percentage of sickled cells Number of hours following withdrawal of specimen								
	0	1	4	8	16	24	36	48	
9/5/48 (prior to second course of BAL therapy)	0	0	0	0	0	0	2	5	
10/4/48			Intramuscular BAL started						
10/7/48 (one hour following injection of 100 mg. BAL in oil i. m.)	0	1*		25*	90				

* These examinations revealed abnormal type of rouleaux.

In order to ascertain the exact role played by this compound in the genesis of her anemia, it was decided to reinstitute BAL therapy in doses similar to those employed previously. Prior in vitro studies were performed with the patient's blood, utilizing saturated aqueous BAL. These are described in detail in a subsequent section (see "Observations"). In brief, they indicated that BAL increased the rate of sickling and the viscosity of the blood, as judged by fresh BAL treated moist preparations and comparative sedimentation rates.

During the ten day period of BAL therapy, there was no appreciable alteration in the volume of packed red blood cells, which remained about 35 ml. per 100 ml.; nor was there any evidence of increased blood destruction. Consistently normal values were obtained for urine and fecal urobilinogen, reticulocyte count, and serum bilirubin. It is of interest that in spite of this the rate of sickling was influenced considerably by the administration of BAL (see table 1). The rate of sickling was markedly accelerated one hour after the administration of BAL as compared with that in specimens of blood just prior to the injection of this drug. Corresponding with this, it was observed that the erythrocyte sedimentation rate was markedly decreased after the administration of BAL, thus confirming in vitro results. The patient showed no evidence of thrombotic phenomena during the trial period with BAL. Her subsequent course has been good with the exception of her mental status, which has remained somewhat clouded. Her blood picture has shown steady improvement and all hemolytic indices remained normal. The patient was recently discharged in good condition and with normal blood values.

OBSERVATIONS

Routine fresh sealed preparations indicated that the patient's red blood cells sickled slowly. No sickle cells were seen even after twenty-four hours. At thirty-

six hours there was two per cent sickling and at seventy-two hours the majority of the red blood cells were sickled. The use of CO₂ or H₂S gas bubbled directly through the blood accelerated the rate of sickling considerably, so that small numbers of red cells became sickled immediately and most were sickled at twenty-four hours. Saturated aqueous BAL acted similarly when one drop was mixed with an equal amount of the patient's blood and a fresh sealed preparation was made. It is interesting that following contact with sulfhydryl compounds many of the

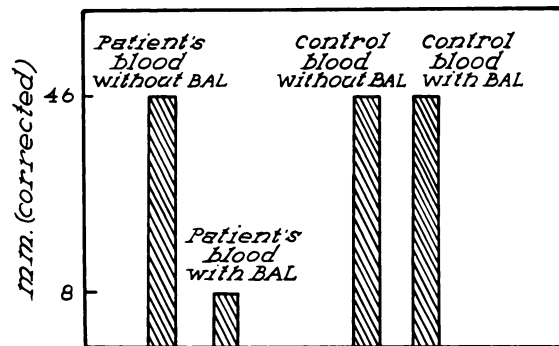


FIG. 1.—THE IN VITRO EFFECT OF BAL (AQUEOUS) ON SEDIMENTATION RATE. (BAL-blood mixtures were prepared by adding one drop of saturated aqueous BAL to 5 cc. of whole blood.)

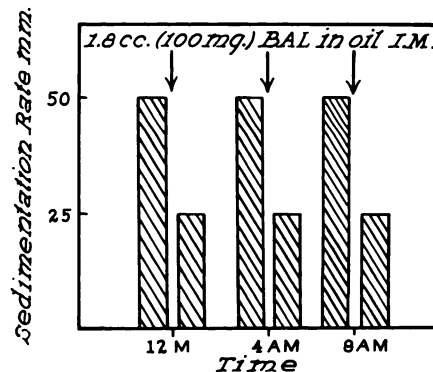


FIG. 2.—EFFECT OF INTRAMUSCULAR INJECTION OF BAL ON SEDIMENTATION RATE IN SUBJECT WITH SICKLE CELL TRAIT.

red blood cells appeared more limp and flabby, and rouleaux were of an abnormal type.

Comparative sedimentation rates carried out on the patient's blood with and without the addition of water soluble BAL indicated that the sedimentation rate of BAL treated blood was decreased more than five fold in comparison to untreated blood (see fig. 1). The mixture of BAL with the blood of normal persons, on the other hand, failed to alter the sedimentation rate. BAL-blood mixtures were prepared by adding one drop of saturated aqueous BAL to 5 ml. of whole blood. Following institution of the second series of BAL injections, sealed preparations

were made one hour after administration of the drug. These were found to sickle considerably more rapidly than did the preparations made before the drug was given (see table 1). Serial sedimentation rates were found to increase and decrease alternately before and after an intramuscular injection of 100 mgm. of BAL in oil (see fig. 2).

DISCUSSION

Study of the present case offers several points of interest. In the first place, it emphasizes the necessity for observations of fresh blood preparations over a period of several days when sickling is being sought. Routine 24 hour specimens showed no sickling in the present case whereas specimens observed at later intervals were definitely positive. This, of course, becomes of less importance as knowledge regarding the known accelerating substances accumulates. In the present case, for instance, it was possible to reduce the time of sickling materially by the use of sulfhydryl compounds. This is in conformity with the findings of Thomas and Stetson.³

It has been demonstrated, furthermore, that the intramuscular administration of BAL accelerates the rate of sickling. Winsor and Burch¹ obtained comparable effects when they utilized methods which increased the CO₂ concentration in patients with sickle cell disease.

The addition of aqueous BAL to specimens of the patient's blood resulted in retardation of the sedimentation rate; similar results were obtained following the intramuscular injection of BAL in oil. The value of the sedimentation rate in detecting sickling was first recognized by Winsor and Burch,¹ who found that the erythrocyte sedimentation rate of the blood of patients with sickle cell anemia could be slowed or accelerated by alternate saturation with carbon dioxide and oxygen. Inhalation of pure oxygen was found to accelerate the sedimentation rate; on the other hand, keeping a tourniquet on the arm for ten minutes retarded the sedimentation rate, as did also rebreathing into a paper bag. Normal blood was found to be affected only slightly by these gases.

The experiments of Thomas and Stetson have indicated that sulfhydryl compounds similarly retarded the sedimentation rate in individuals with sickle cell disease. Of special interest in the present case was the alteration in sedimentation rate following exposure of the patient to BAL. This occurred, however, in the absence of any of the pathognomonic criteria of sickle cell anemia.

The possible development of sickle cell disease in Negroes harboring the sickle cell trait is a question which has evoked some divergence of opinion. The trait is said by Bauer⁵ to change occasionally to the disease under certain conditions of anoxemia and stress if a large number of red blood cells are caused to sickle. Such conditions would include local or general anoxemia resulting from infectious disease, surgical procedures, or other conditions known to slow the circulation of the blood, such as pregnancy and blood transfusion. On the other hand, Wintrobe⁶ and Singer, et al.⁷ insist that sickle cell trait and sickle cell disease are separate entities, and that carriers of the trait never acquire sickle cell disease. Singer and associates⁷ studied the comparative survival rates in normal individuals of trans-

fused cells from persons with the trait and with sickle cell anemia and found that the former survived as long as did normal red blood cells, whereas the latter survived a much shorter period of time. On the basis of these studies, they have suggested that sickle cell anemia develops because of an alteration in the red blood cell cytoskeleton which is qualitatively different from the structural anomaly responsible for the sickling phenomenon.

The etiology of the anemia in the present case was not definitely ascertained. Administration of BAL to the patient did not produce any evidence of hemolysis or any of the other characteristics of sickle cell disease. What role, if any, the compound played in relation to the anemic and thrombotic episodes earlier in her clinical course is difficult to determine. It is quite probable that administration of the drug was in no way involved. The manner in which her anemia developed, i. e., without any evidence of hemolysis and concomitant with thrombophlebitis and a consolidative pulmonary process, followed shortly thereafter by a severe renal infection, all suggest an anemia of infection rather than anemia due to blood loss, which is the only other possibility which comes to mind. The low plasma iron might have been found in either case but the absence of hypochromia and microcytosis of the red blood cells, and the lack of any clinical evidence or history of blood loss makes the former possibility the more probable.

SUMMARY

The effects of the intramuscular administration of BAL in a Negro harboring the sickle cell trait have been presented. It was observed that the rate of sickling was accelerated and the erythrocyte sedimentation rate was retarded in the presence of BAL both in vitro and apparently in vivo. However, the administration of BAL produced none of the pathologic sequelae characteristic of sickle cell disease.

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