RESPONSES TO CORTICOTROPIN (ACTH) AND CORTISONE IN THROMBOCYTOPENIC STATES

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SPLENECTOMY, considered to be the treatment of choice in idiopathic thrombocytopenic purpura (ITP), has not been attended by uniformly favorable results. Corticotropin (ACTH) and cortisone have recently been found to be effective in some instances of this disorder. This paper summarizes observations on 12 patients with thrombocytopenia of various types, and demonstrates the ability of the steroid hormones to reduce hemorrhagic tendencies even in the absence of a platelet response.

RESULTS

Of the 12 patients, seven had ITP (Table 1), three had thrombocytopenia following drug ingestion, one had thrombocytopenia associated with disseminated lupus erythematosus, and one had chronic lymphocytic leukemia treated by irradiation therapy (Table 2). All received corticotropin or cortisone or a combination of the two.

A sustained clinical and hematologic remission was not obtained in any of the seven patients who had ITP. Two of these received corticotropin alone. One experienced prompt cessation of the bleeding tendency unassociated with a rise in platelets. The other responded with a transient improvement in the hemorrhagic diathesis and a rise in platelets, but relapsed promptly on withdrawal of the drug. This response was obtained in a four year old boy (case 4) who had had a sudden onset of petechiae and epistaxis. The platelet count initially was 61,000 per cu. mm. (Dameshek). On the fourteenth day of treatment the platelet count was 536,000 per cu. mm. Treatment was stopped at this time, and approximately four weeks later the platelet count had dropped to 106,000 per cu. mm.

Four other patients with ITP also received cortisone alone. One responded rapidly with disappearance of purpura and a rise in platelets but relapsed two weeks after therapy was discontinued. Three responded clinically with clearing of the petechiae and cessation of the bleeding, but showed no platelet rise for periods of seven months, 36 days and 21 days, respectively.

The seventh patient with ITP was treated with corticotropin intravenously for one week and experienced remission of all vascular phenomena but failed to exhibit an increase in platelets during a subsequent 55 day course of cortisone.

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Three patients had thrombocytopenia resulting from drug idiosyncrasy. Two of these patients were treated with corticotropin and the third with cortisone. All experienced prompt clinical and hematologic remissions which have persisted 25, 19 and 3 months respectively. An example of the dramatic results occasionally obtained in this type of case was manifested in an 80 year old man (case 10). He had superficial ecchymosis, and hemorrhages into the tissues of the neck and tongue had developed so that he was unable to swallow. The initial platelet count was 24,000 per cu. mm. (Rees-Ecker). Eighteen hours after corticotropin was begun, the tongue was smaller and he was able to swallow, although the platelet count was unchanged. On the sixth day of treatment the platelet count had reached 188,000 per cu. mm. (Rees-Ecker). He has remained well for a subsequent period of one year.

The patient with thrombocytopenia associated with disseminated lupus erythematosus showed a satisfactory response. There was a complete cessation of all bleeding and the platelets returned to a normal level. She was maintained in this remission for a period of 13 months on continued cortisone therapy.

The patient with thrombocytopenia resulting from a combination of chronic lymphocytic leukemia and irradiation therapy obtained relief of active bleeding without significant platelet elevation coincident to corticotropin administration.

DISCUSSION

In this group, steroid therapy was disappointing as a means of inducing complete and permanent remission in ITP. In five of the six patients with "chronic" ITP no hematologic remission was obtained. In the sixth patient, the platelets rose to a normal level during treatment but decreased again when therapy was discontinued. The only patient with "acute" ITP responded on several separate occasions with an adequate platelet elevation which dropped each time to pre-treatment levels shortly after stopping the drug.

In the three instances of thrombocytopenia secondary to drug sensitivity, cortisone or corticotropin therapy was followed by an excellent clinical and hematologic response. Whether this was due entirely to the drug or in large part to withdrawal of the offending drug cannot be stated.

All patients studied experienced relief of the bleeding phenomena and in three this was dramatic. Improvement in capillary resistance as measured by the tourniquet test (Rumpel-Leede), was noted in all patients but could not be correlated with platelet levels or responses. Only two patients in the ITP group showed a prompt and significant platelet rise during treatment. Two patients subsequently had splenectomies. One of these had responded with a complete remission while receiving cortisone but relapsed later. After splenectomy, there was a remission which has lasted seven months. The other patient had had no hematologic improvement while on cortisone, but following splenectomy a satisfactory platelet rise occurred.

Conclusions derived from early reports concerning the use of steroids, although encouraging, have been justifiably cautious. Bethell, Miller and

Meyers[1] were the first to report favorable clinical and hematologic responses in six patients with ITP who were treated with corticotropin. Meyers, Miller, Linman and Bethell[2] reported further observations on these and 11 additional patients, some of whom were treated with cortisone as well. In 12 of their 17 patients results were described as excellent. Five of their patients continued in remission for periods of 16 to 22 months. Robson and Duthie[3] reported clinical improvement without sustained platelet response in two patients with ITP. Faloon, Greene and Lozner[4] noted complete remission with corticotropin in one of five patients, and varying responses to corticotropin or cortisone in the remaining four patients. They noted improvement in vascular resistance in all cases preceding the rise in platelets, and in some instances, independent of it. Jacobson and Sobier[5] reported prompt but transient platelet responses to normal levels in three patients with ITP. Wintrobe and others[6] obtained temporary remission with corticotropin in one patient. Hyman[7] obtained persistent remission in one patient with corticotropin and transient response in another. Wilson and Eiseman[8] observed 12 patients and noted sustained improvement in three and transient responses in two. Stefanini et al.[9] treated 11 patients suffering from ITP and obtained no permanent remissions. They concluded that these hormones reduced the spontaneous bleeding manifestations, improved capillary resistance, shortened the bleeding time, and prolonged the phase of initial vasoconstriction following incision of the skin.

The mechanisms responsible for thrombocytopenia in ITP are obscure. Several different theories have been suggested. Thrombocytopenia has been attributed to: (1) sequestration or phagocytosis of platelets by the spleen; (2) the action of a hypothetical humoral substance produced in the spleen, or elsewhere, capable of suppressing megakaryocytic activity; and (3) a thrombocytopenic factor in plasma which damages circulating platelets and possibly also suppresses the megakaryocytes. Current studies have served to emphasize the latter concept that immunologic factors play a major part in many cases of ITP.[10-12] An immunologic mechanism has also been suggested as an etiologic factor in purpura secondary to certain drugs. For instance, platelet agglutination and lysis, in vitro, by the addition of Sedormid to blood of patients who have recovered from Sedormid purpura, have been described.[13] This was found to result from a plasma factor acting in the presence of Sedormid. A similar mechanism has been observed in purpura due to quinidine. It is generally conceded that the thrombocytopenia in leukemia is predominantly due to a mechanical displacement of the megakaryocytes.

There is little direct evidence that corticotropin and cortisone can directly affect any of these pathogenetic mechanisms. Furthermore, it is difficult to evaluate the actual role of these drugs in ITP since spontaneous remissions can occur. It is necessary to consider the effects of these steroids with regard to two aspects of thrombocytopenia, namely, their effect on capillary resistance, and their effect on platelet production. It has been repeatedly observed that improvement in hemostasis and vascular resistance in ITP treated with corticotropin and cortisone may occur despite the persistence of thrombocytopenia.

Table 1

Effect of Steroid Therapy in Seven Patients with Idiopathic Thrombocytopenic Purpura

Case No. and Sex	Age in years	Diagnosis	Therapy mg./day No. days	Platelet count before therapy	Platelet count after therapy (day)	Bleeding phenomena		Remarks
						Before	After	
1 M	11	Idiopathic thrombopenic purpura	Cortisone 200 mg/7 da. 100 mg/14 da. 75 mg/14 da.	10,000	18,000 (7)	++	+	No response; remission followed splenectomy. (1 mo.)
2 F	8	Idiopathic thrombopenic purpura	Cortisone 100 mg/9 da. 50 mg/5 da.	46,000	140,000 (14)	++	0	Clinical and hematologic response with prompt relapse. Remission following splenectomy. (7 mo.)
3 F	21	Idiopathic thrombopenic purpura.	ACTH 80 mg/10 da.	100,000	100,000 (10)	++++	0	Prompt clinical remission. Gradual platelet rise over 1 yr. period.
4 M	4	Idiopathic thrombopenic purpura	ACTH 60 mg/4 da. 40 mg/7 da.	61,000	536,000 (14)	++	0	Complete remission. Relapse in 1 mo.
5 F	17	Idiopathic thrombopenic purpura	Cortisone 200 mg/7 da. 100 mg/14 da.	80,000	33,000 (21)	++	0	Petechiae disappeared. No hematologic improvement.
6 M	30	Idiopathic thrombopenic purpura	ACTH I.V. 20 mg/6 da. cortisone 200 mg/10 da. 100 mg/14 da. 75 mg/21 da.	11,000	33,000 (31)	++	+	Petechiae improved. No hematologic changes.
7 F	15	Idiopathic thrombopenic purpura	Cortisone 200 mg/21 da. 100 mg/7 da.	17,000	40,000 (14)	++	0	Petechiae disappeared. No significant platelet rise.

Table 2

Effect of Steroid Therapy in Five Patients with Secondary Thrombocytopenic Purpura

Case No. and Sex	Age in years	Diagnosis	Therapy mg./day No. days	Platelet count before therapy	Platelet count after therapy (day)	Bleeding phenomena		Remarks
						Before	After	
8 F	15	Disseminated lupus erythematosus	ACTH 40 mg/10 da.	20,000	192,000 (8)	++++	0	Remission maintained 1 yr. Patient later placed on maintenance cortisone.
9 M	45	Drug idiosyncrasy	ACTH 80 mg/4 da. 40 mg/2 da.	< 10,000	100,000 (9)	++++	0	Remission maintained 25 mo.
10 M	80	Drug idiosyncrasy	ACTH 100 mg/5 da. 40 mg/3 da.	24,000	188,000 (6)	++++	0	Complete remission—sustained for 1 yr.+.
11 F	48	Drug idiosyncrasy	Cortisone 300 mg/7 da. 200 mg/4 da. 100 mg/10da.	< 10,000	100,000 (10)	++++	+	Complete remission—3 mo. follow-up.
12 M	63	Chronic lymphocytic leukemia—irradiation thrombopenia	ACTH I.V. 20 mg/10 da.	20,000	20,000 (10)	++++	0	Clinical remission. No platelet rise. 3 mo. follow-up.

This suggests a dual effect of these drugs on thrombocytopenic purpura. Robson and Duthie[3] have demonstrated increased capillary resistance following various kinds of stress and trauma which they attributed to adrenal cortical activity. Improvement in vascular resistance may also occur following splenectomy in the absence of a platelet response. It has been repeatedly observed in patients with ITP receiving adrenal steroids, that capillary resistance increases prior to, or in the absence of, a rise in platelets. Corticotropin and cortisone have been shown to lessen vascular permeability in various conditions, although capillary permeability itself has not been incriminated in ITP.[14] The adrenal steroids in some way alter the capacity of tissues to react characteristically to the irritative action of antigen-antibody combinations. These drugs have been found to induce remission in allergic purpura not associated with thrombocytopenia. Should a state of hyperimmunity involving the capillary walls underlie some of the phenomena in thrombocytopenic purpura, a passive mode of action of these hormones could be postulated without regard to the platelet level.

The second aspect of thrombocytopenia as related to corticotropin and cortisone involves their action on platelet production. Their effect has been irregular although reports in the literature indicate that some patients with thrombocytopenic states respond to the drugs with an increase in platelet production. It is possible that these hormones control an "immuno-thrombocytopenia" by suppression of a platelet antibody, similar to their effect in certain cases of acquired hemolytic anemia associated with a positive antiglobulin test. Harrington and his group[12] observed a complete remission in ITP from cortisone which was associated with disappearance of the thrombocytopenic factor. Emphasizing another possible mode of action, Bethell[1] has stated that the spleen exerts a "regulatory action susceptible to derangement" on the maturation and release of thrombocytes and that this function may be under the control of the adrenal cortex. Another mechanism postulated to explain the action of corticotropin and cortisone involves their capacity to stimulate myeloid elements. Harrington[12] mentioned two patients without demonstrable platelet agglutinins who responded to these agents. He presumed in these cases that the hormones stimulated an increased rate of platelet formation from megakarocytes. It is possible, as Meyers[2] suggests, that the adrenal hormones in thrombocytopenia restore "hematopoietic equilibrium" through a combination of effects including non-specific action on capillary fragility, modification of responses to antigen-antibody combinations and stimulation of the megakaryocytes.

SUMMARY AND CONCLUSIONS

Observations were made on 12 patients with thrombocytopenia of various etiology who were treated with corticotropin or cortisone.

Improvement in capillary fragility and bleeding phenomena occurred in all seven patients with ITP. Five showed no rise in platelets. Two exhibited a transient rise in the platelet count, but relapsed when therapy was discontinued.

Satisfactory clinical and hematologic remission was demonstrated in each

of three patients with purpura secondary to drug sensitivity, and in a patient with acute lupus erythematosus.

Complete cessation of the hemorrhagic tendency, without a concomitant platelet rise, occurred in one patient with chronic lymphocytic leukemia.

Corticotropin and cortisone exert a beneficial effect on capillary fragility and bleeding phenomena in various types of thrombocytopenia. The improvement is not necessarily associated with an increase in circulating thrombocytes.

Observations indicate that these agents are useful in controlling severe bleeding in ITP, in secondary thrombocytopenia and in the preparation of patients for splenectomy. As a means of inducing a permanent remission in ITP, however, steroid therapy has been disappointing.

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