STUDIES ON THE EARLY POSTOPERATIVE REDUCTION OF PROTHROMBIN IN THE JAUNDICED AND BILIARY FISTULA PATIENT WITH SPECIAL REFERENCE TO ANESTHESIA *

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The necessity of vitamin K for the formation of plasma prothrombin is now well established (1). Abundant presumptive evidence now at hand implicates the liver as the site of prothrombin formation (2). Thus at least two factors are necessary for the maintenance of normal plasma prothrombin. One is the adequate absorption of vitamin K or its substitutes (3), and the other is the intact liver mechanism essential for prothrombin production (4). The physiological process by which prothrombin is activated by vitamin K is not clearly understood.

In the course of study of prothrombin deficiency in patients with jaundice, Stewart (5) has shown that a temporary depression of plasma prothrombin frequently occurs during the early postoperative period in these patients. We have observed this same phenomenon. This postoperative fall of prothrombin has in some patients been sufficient to give rise to brisk hemorrhage, and this reduction of prothrombin may occur even though any initial prothrombin deficiency has been corrected by preoperative vitamin K therapy.

The data presented here is a preliminary report concerned with the study of the nature of the postoperative depression of plasma prothrombin and its possible relationship to the anesthetic agent used.

Methods of Study

Two groups of surgical patients were selected for these studies. Group one consisted of patients with normal plasma prothrombin who underwent major surgical operations under various anesthetic agents. Of approximately fifty such patients studied, ten representative of the group are presented here (Table I). Group two (Table II) includes all the patients with prothrombin deficiency who underwent a major surgical procedure during the course of this study. The plasma prothrombin was determined by a modified one-stage technique (6) and the values are expressed in terms of per cent of normal plasma. Prothrombin determinations were made at least once preoperatively and daily postoperatively for four days or longer in each case.

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TABLE I

PROTHROMBIN STUDIES ON SURGICAL PATIENTS IN WHOM NO PRE-OPERATIVE PROTHROMBIN DEFICIENCY WAS PRESENT

Case No.	Diagnosis	Surgical Procedure	Anesthetic Agent	Total Period of Anesthesia	Postoperative Prothrombin
1	Left frontal lobe tumor	Craniotomy with partial extirpation of tumor	Ether	4 hrs.	No reduction
2	Right mastoiditis	Radical mastoidectomy	Avertin supplemented by ethylene-oxygen	1 hr., 55 min.	"
3	Acute osteomyelitis of skull	Partial ostectomy of skull	Avertin supplemented by ethylene-oxygen	3 hrs., 25 min.	"
4	Carcinoma of stomach	Subtotal gastrectomy	Novocain local with splanchnic block	3 hrs.	"
5	Islet cell tumor of pancreas	Resection of tumor	Nupercaine spinal supplemented by ethylene-oxygen	2 hrs.	"
6	Spinal cord tumor	Laminectomy	Ethylene-oxygen and ether	4 hrs., 45 min.	"
7	Splenomegaly	Splenectomy	Ethylene-oxygen and ether	1 hr., 40 min.	"
8	Carcinoma of breast	Radical mastectomy	Ethylene-oxyxen	1 hr., 50 min.	"
9	Carcinoma of stomach	Total gastrectomy	Novocain local and splanchnic block	2 hrs., 40 min.	Fell to 28 per cent. by 12th day. Given no Vitamin K during this P.O. interval
10	Pulmonary tuberculosis	2nd stage thoracoplasty	Ethylene-oxygen	1 hr.	No reduction

PRESENTATION OF DATA

In Table I is presented a brief description of ten patients selected from group 1. It will be seen that only one patient showed any significant depression of plasma prothrombin during the postoperative period. This patient (case 9), subjected to total gastrectomy, showed no depression of plasma prothrombin during the first four postoperative days. Because of the restricted intake of food by mouth the prothrombin was again determined on the 12th day when it was found to be 28 per cent. of normal. The delay in the postoperative appearance of prothrombin deficiency in this case suggests that this reduction was due to a nutritional insufficiency (7) and not to either the anesthetic agent or the operation *per se*.

In Table II are presented data obtained on seven patients who were

TABLE II

PROTHROMBIN STUDIES ON SURGICAL PATIENTS IN WHOM INITIAL PROTHROMBIN DEFICIENCY WAS PRESENT

Case No.	Diagnosis	Surgical Procedure	Anesthetic Agent	Total Anesthesia Period	Prothrombin Time as Per Cent. Normal		Vitamin K (Naphthoquinone)		PO Days Prothrombin Remained Normal	Remarks
					Initial	Immed. Preop.	Dose /day	Days Given		
1	Stricture of common duct	Laparotomy	Nupercaine 10 cc. spinal supplemented by ethylene-oxygen	1′ 30″	15	100	8 mgm.	5	5	Prothrombin fell to 80 per cent. 6th day, to 40 per cent. 7th day. No food by mouth
2	Common duct stone	Choledocholithotomy and cholecystectomy	Novocain spinal supplemented by ethylene-oxygen	3′ 55″	100	100	8 mgm.	1	1	Prothrombin time dropped to 65 per cent. by 1st P.O. day
3	Common duct stone	Choledocholithotomy and cholecystectomy	Novocain spinal supplemented by ethylene-oxygen	3′ 30″	45	100	8 mgm.	7	7	Developed peritonitis; no food by mouth for 8 days
4	Obstructive jaundice (Carcinoma, head of pancreas)	Cholecystgastrostomy	Nupercaine spinal 14 cc. supplemented by ethylene-oxygen	1′ 30″	75	100	8 mgm.	4	0	No P.O. fall of prothrombin: oral feedings begun 4th day
5	Obstructive jaundice (stricture common duct)	Release of adhesion	Novocain spinal	1′ 20″	80	100	8 mgm.	3	0	No P.O. fall of prothrombin; oral feedings begun 4th day
6	Biliary fistula	Reconstruction of common duct	Ethylene-oxygen	4′ 10″	35	100	8 mgm.	2	1	Prothrombin 80 per cent. normal 1st P.O. day, 50 per cent. 2nd day. Naphthoquinone given
7	Acute hepatitis	Laparotomy with cholecystectomy	Novocain spinal supplemented by ethylene-oxygen	3′ 30″	50	100	6 mgm.	2	1	Prothrombin fell to 65 per cent. by 2nd P.O. day; naphthoquinone then given

found to have initial plasma prothrombin deficiencies. Each of these patients was then given a vitamin K substitute, 2-methyl-1, 4-naphthoquinone, in doses of 2 mgm. with 0.6 gm. bile salts (Lilly) four times daily during their preoperative period. In all of these patients the plasma prothrombins were normal within 36 hours after naphthoquinone therapy was instituted. The naphthoquinone in each case was withheld during the postoperative period until appreciable drops in the plasma prothrombin levels could be demonstrated. During the postoperative period 5 of the 7 patients presented in Table II showed a reduction of plasma prothrombin during their early postoperative periods. Oral feedings which included vitamin K-containing foods were begun on the fourth postoperative day of cases 4 and 5 of this group, and since no reduction of prothrombin was observed by this time, further studies were not carried out on these cases.

COMMENT

From the data in Table I it is obvious that no significant reduction of plasma prothrombin could be demonstrated in the early postoperative periods of patients whose initial preoperative prothrombin concentrations were normal. This observation is supported experimentally by Warner and Rhodes (2) who were unable to effect measurable prothrombin changes in normal dogs subjected to prolonged ether anesthesia or to acute severe blood loss.

However, as shown in Table II, patients who have had an initial prothrombin deficiency, show a postoperative fall, even though the naphthoquinone has been given during the preoperative period with elevation of prothrombin to 100 per cent. It may be that the normal patient has a reserve of potential prothrombin not detectable by this method of determination. This reserve might be made available to the blood stream during the postoperative period thus masking any effect of surgery or anesthesia. The patient with initial prothrombin deficiency, even though treated so that the plasma prothrombin has returned 100 per cent., still might have no reserve. Thus any effect of either the surgical procedure or the anesthetic agent in these patients would be more readily apparent. However, the data in case 9 is suggestive that severe blood loss in itself will not significantly alter the prothrombin level in a patient whose pre-hemorrhagic prothrombin concentration was dangerously reduced. In this case a severe gastrointestinal hemorrhage, occurring six hours after a prothrombin level of 28 per cent. was found, failed to produce any change in the prothrombin concentration within one hour after this episode.

Stewart and Rourke (1) have shown that the postoperative depression of prothrombin may occur in the prothrombin deficient patient treated with vitamin K whose surgery was performed entirely under local novocain anesthesia. Our data, while not permitting a definite conclusion on this point, would seem to support the findings of these

workers. In all but one of our patients described in Table II spinal anesthesia was the primary anesthetic agent employed while ethylene-oxygen was used only in supplementary role, indicating that the prothrombin fall following surgery is not dependent upon the use of a general anesthetic agent.

A prothrombin reading of 100 per cent. indicates that the clotting time of the plasmas of the control and the abnormal are equal. As indicated above this reading does not imply that the quantity of potential prothrombin reserve is equivalent. Since none of these patients presented in Table II received food by mouth during the first four postoperative days it is apparent that the prothrombin levels in these cases must have been maintained by the reserves of potential prothrombin present in the body at time of surgery. It is very interesting then that a close correlation exists between the amount of preoperative naphthoquinone given and the rapidity with which the postoperative falls in prothrombin occurred. Case 3 received 64 mg. of naphthoquinone preoperatively, the prothrombin levels remained normal for seven days after operation; while cases 2, 6 and 7, all receiving less than 20 mgm. preoperatively, developed a significant fall in prothrombin within two days after operation.

The data from these cases would indicate that the early postoperative fall in prothrombin is caused primarily by inadequate administration of vitamin K before operation. It would seem that anesthesia, operative trauma and hemorrhage play no significant role in the production of postoperative prothrombin deficiency.

REFERENCES

1. Stewart, J. D., and Rourke, G. M.: Control of Prothrombin Deficiency in Obstructive Jaundice, J. A. M. A. 113: 2223 (Dec. 16) 1939.
2. Warren, R., and Rhoads, J. E.: The Hepatic Origin of the Plasma-prothrombin, Am. J. Med. Sci., 198: 193 (Aug.) 1938.
3. Brinkhaus, K. M.; Smith, H. P., and Warner, E. D.: Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula, Am. J. Med. Sci. 196: 50 (July) 1938.
4. Pohle, F. J., and Stewart, J. K.: Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, J. Clin. Invest. 19: 365 (March) 1940.
5. Stewart, J. D.: Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, Ann. Surg. 109: 588 (April) 1939.
6. Allen, J. G.; Julian, O. C., and Dragstedt, L. R.: The Use of Serial Dilution in the Determination of Prothrombin by the One-stage Technique. In press.
7. Kark, R., and Lozner, E. L. Nutritional Deficiency of Vitamin K in Man, Lancet 2: 1162, (Dec. 2) 1939.