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THE USE OF VITAMIN K AND BILE SALTS IN THE PREVENTION AND CONTROL OF THE HÆMORRHAGIC DIATHESIS IN OBSTRUCTIVE JAUNDICE

(PRELIMINARY REPORT)

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THE present report records the therapeutic value of vitamin "K" and desiccated bile in 10 cases of jaundice associated with prothrombin deficiency and resulting in the hæmorrhagic tendency. It is presented in support of earlier observations of Warner *et al.*, and others,[26 to 32] who have suggested its clinical use, although a comparable deficiency state has been recognized in cattle for some years.[17, 18] The cases under study are those which presented in the medical and surgical wards of the Montreal General Hospital during the first six months of 1939.

In our early cases the prothrombin time and the coagulation time were calculated by the method of Howell and Duke, respectively, as outlined in most standard textbooks. In subsequent cases the prothrombin or clotting time was studied by Quick's method[15] which is considerably more accurate. This method is simple and affords an indirect measurement of the plasma prothrombin level, which Snell[25] has pointed out varies inversely with the clotting time. The vitamin K was a preparation made from alfalfa and was used in both capsule and liquid form. The liquid was well tolerated by mouth, but in some cases was given by means of a duodenal tube.

CASE REPORTS STUDIED

CASE 1

A 73-year-old Chinaman was admitted to hospital with complaints of pain in the right upper quadrant and flatulence of one week's duration. Examination revealed that the scleræ were icteroid and the liver just palpable. There was also a history of jaundice in June, 1938. Laboratory investigation showed an increased van den Bergh reaction of 11 to 13 units (0.2 to 0.5 units normal). The blood sugar, phosphatase, and galactose tolerance tests were normal. The coagulation time (Duke) was increased to 16 minutes (normal 5 to 10 minutes) and prothrombin time (Howell) was increased to 225 seconds (60 to 105 seconds normal). He was placed on 1,800 units (Ayerst) of vitamin K and 1 g. of bile salts per day. In three days the above values had returned to normal limits. A clinical diagnosis of cholelithiasis was made but operation was not attempted.

CASE 2

A 57-year-old white female was admitted because of pain in the right upper quadrant. There had been recurrent attacks for the past three years. With this attack of pain there had been associated nausea and vomiting, flatulence and constipation. The pain was sharp in nature and referred to the back and shoulder. She had never been jaundiced, but for the past week had noted icterus and that her stools were light coloured. Laboratory investigation revealed normal blood chemistry, except for an elevated van den Bergh reaction of 3.0 units. The coagulation time was prolonged to 28 minutes and the prothrombin time to 128 seconds, or by Quick's method, to 28 seconds (normal, 15 to 22 seconds). On 2,400 units (Ayerst) of vitamin K and 2 g. of bile salts per day the coagulation time returned to 12 minutes and the clotting time (Quick) to 18 seconds. The time-interval required was two weeks but the patient had considerable vomiting and did not retain all of the vitamin K, although some was given latterly by duodenal tube. In the course of a blood transfusion an immediate reaction was encountered. As a result there was temporary severe renal damage and after recovery operation was postponed. The gall-bladder symptoms subsided.

CASE 3

A 74-year-old white male was admitted July, 1938, with a severe attack of gall-bladder colic. After improvement there was a recurrence of symptoms in March, 1939. Jaundice occurred and the liver enlarged to two fingers' breadths below the right costal margin. The van den Bergh was increased to 7.0 units, the coagulation time to 22 minutes, and the prothrombin time to 265 seconds. On 1,800 units of vitamin K and 2 g. of bile salts of bile salts per day the coagulation and prothrombin times returned to normal limits in 5 days. Cholecystectomy was performed with no abnormal bleeding.

CASE 4

A 43-year-old Chinaman was admitted with an attack of cholelithiasis. The van den Bergh was increased to 3.0 units, but the coagulation and clotting times were

only slightly disturbed. The obstruction was presumably incomplete as there was bile in the stools; it is also of note that a normal diet was being maintained. Vomiting, however, ensued and a normal diet could not be taken. The coagulation time increased to 26 minutes and the prothrombin time to 110 seconds. On 1,800 units and 2 g. of bile salts per day the coagulation and prothrombin time decreased to normal limits in 11 days. Operation was performed with no abnormal bleeding. Post-operative vomiting was of short duration and a normal diet was instituted. In the presence of bile drainage of 200 to 520 c.c., the coagulation and prothrombin times were maintained at normal levels with the administration of bile alone.

CASE 5

A 75-year-old white male was admitted with a history of jaundice in 1938. At that time the van den Bergh was increased to 5.0 units, the phosphatase was elevated to 110 units (11 to 13 units, normal), and there was diminished tolerance to the glucose meal. The prothrombin time was also increased to 120 seconds. His symptoms subsided but he continued to lose weight and was readmitted with a recurrence of jaundice. The van den Bergh was increased to 8.0 units, the phosphatase to 48 units and the cholesterol to 0.555 mg. per cent. The coagulation time was 18 minutes and the prothrombin time 180 seconds. On 1,800 units of vitamin K and 1 g. bile salts per day the coagulation and prothrombin times returned to normal in 10 days. There was no abnormal bleeding following or during a cholecyst-jejunostomy. A diagnosis of carcinoma of the head of the pancreas was made.

CASE 6

A female aged 63 was admitted with complaints of jaundice and a large nodular liver was found. A diagnosis of carcinoma of the stomach with secondary metastases and obstructive jaundice was made. The van den Bergh was 9.0 units and the phosphatase increased to 43 units. The coagulation time was 35 minutes and the clotting time (Quick) 55 seconds. Following treatment with 3,200 units (Ayerst) and 3 g. of bile salts the coagulation and clotting times returned to normal limits. A laparotomy was performed; no post-operative bleeding occurred. After the wound had healed the vitamin K and bile salts were discontinued and the clotting time (Quick) again increased to abnormal limits. This case was an inoperable carcinoma of the head of the pancreas and no manipulation had been done at the time of the operation.

CASE 7

A 69-year-old male was admitted with complaints of jaundice of 5 days' duration, pain in the epigastrium, and clay-coloured stools. He had had similar attacks for a period of two or three years. On examination he appeared deeply jaundiced and had lost considerable weight. The liver was markedly enlarged. The urine and stools contained bile. The van den Bergh was increased to 6.0 units but the plasma phosphatase was normal. He was able to tolerate a normal diet, and under observation the attack subsided as well as the jaundice. The coagulation time and prothrombin time were normal. The absence of prothrombin disturbance was presumably due to the fact that the patient was able to utilize the vitamin K in his diet in the presence of sufficient bile, as his obstruction was incomplete. He was discharged but readmitted later for operation. The jaundice had subsided, the stools were a normal colour and he was able to take a normal diet. Again the clotting time was normal. A cholecystectomy was performed and a T-tube placed in the common duct for drainage. On account of an abnormal flow of bile the common duct was visualized by means of uroselectan. This revealed obstruction to the uroselectan into the duodenum. The clotting time after the establishment of the above facts was markedly disturbed, being prolonged to 55 seconds (Quick). Vitamin K and bile salts were not given, as the patient developed an upper respiratory infection followed by a bronchopneumonia and operation was out of the question.

CASE 8

A 45-year-old white female was admitted with symptoms of gall-bladder colic and jaundice. The obstruction was not complete and the clotting time (Quick) was recorded as normal. Operation was performed and was followed by excessive bleeding from the wound. Because of this serious bleeding a blood transfusion was given, but before the transfusion the clotting time was found to be increased to 38 seconds. Vitamin K, 10,000 units (Squibb) and 2 g. bile salts were administered by duodenal tube and the hæmorrhage was controlled in 36 hours. Vitamin K, 3,000 units (Squibb), and bile salts 2 g. were continued for 10 days after operation and further bleeding was controlled without the aid of blood transfusion. During this period the clotting time remained normal.

CASE 9

A 58-year-old white male was admitted with symptoms of cholelithiasis and jaundice. This was complicated by hypertensive cardiovascular disease. The clotting time was prolonged to 30 seconds. The patient had been given small doses of vitamin K before admission plus bile salts. With a large dose of vitamin K, 10,000 units (Squibb) and 2 g. of bile salts, the clotting time returned to normal in 24 hours; this, however, was assisted by a small blood transfusion. On account of his critical condition, blood transfusions were given in addition to vitamin K therapy. The post-operative course was uneventful.

CASE 10

A 27-year-old white male was admitted with complaints of severe pain in the epigastrium of 8 hours' duration. He had had similar attacks over a two-month period, associated with constipation and flatulence. On admission there was no jaundice but the abdomen was acutely tender, with the point of maximum tenderness over the gall-bladder region. Jaundice developed and the van den Bergh rose to 7.0 units. The coagulation time was increased to 15 minutes and the clotting time (Howell) to 150 seconds. He was placed on vitamin K 2,400 units (Ayerst) and 2 g. of bile salts per day. In 72 hours the clotting time (Howell) had decreased to 105 seconds, but the coagulation time was elevated to 19 minutes. On the following day operation was performed with no abnormal bleeding. A chronic pancreatitis with a chronic cholecystitis and stone in the common duct was found. Following operation the jaundice disappeared and the blood chemistry remained normal. While the clotting time remained within normal limits, the coagulation time continued to be elevated to 19 minutes. In all the other cases the latter value became normal shortly after the establishment of a normal clotting time. We therefore consider the response in this case to be somewhat unsatisfactory.

DISCUSSION OF THE LITERATURE

The problem of bleeding in jaundiced patients, particularly those with the obstructive type, has been for years a distressing problem and has served as a basis for numerous studies. Fairly reliable methods for the study of fibrinogen and calcium are available but these constituents are seldom greatly disturbed. Fibrinogen is generally normal, often elevated,[1, 2, 3] and only when there is extensive liver damage is it diminished.[4, 5] Calcium, on the other hand, is rarely found disturbed in obstructive jaundice.[6 to 11]

Some feel that although a functional deficiency of calcium exists[12] it is not related to the bleeding tendency.

The generally accepted theory of blood coagulation is that prothrombin reacts with thromboplastin and calcium to form thrombin, which in turn, reacts with fibrinogen to form fibrin.[13] Assuming that calcium and fibrinogen were normal in most cases, Quick[14] studied prothrombin and revealed that this constituent was quantitatively disturbed. This was confirmed by Smith *et al.*[16] The methods evolved by these workers[15, 16] are indirect measurements of prothrombin, but Quick's method is the most useful for the average clinical study. The method is also much more reliable than the test outlined by Howell.

In another field of investigation Schofield[17] pointed out a hæmorrhagic disease in cattle due to feeding improperly cured sweet clover. Roderick[18] demonstrated that this clotting defect was due to a reduction in prothrombin. A number of investigators also have shown a hæmorrhagic disease in chicks when fed a low fat diet.[19 to 23] Here as in sweet clover disease there is a deficiency of prothrombin, but, as Dam showed, this can be controlled or prevented by the administration of hog liver fat,[23] or by feeding alfalfa.[24]

Quick[14] was the first to demonstrate that a similar deficiency of prothrombin exists in various types of jaundice, and this was confirmed by Smith *et al.*[16] Subsequent work has shown that the hæmorrhagic disease is due to a deficiency of a fat-soluble substance now known as vitamin K. Its distribution, physical, and chemical properties are fairly well known,[25] and reports of its use in the treatment of the hæmorrhagic diathesis,[26 to 32] associated with obstructive jaundice, indicate that the substance is of considerable value in preventing and controlling post-operative bleeding, but the beneficial effect is obtained only in the presence of bile.

COMMENT

The delayed clotting time in the foregoing 10 cases indicates that the plasma prothrombin levels were disturbed, except when the obstruction to bile flow was incomplete and a normal diet was being maintained. In 9 cases the clotting time was prolonged but returned to normal on vitamin K therapy with the addition of bile salts. There was one failure for which no adequate explanation is offered.

In all these cases there is presumably a failure to absorb fat-soluble substances when there is exclusion of bile from the intestinal tract. Some common causes of this type of obstruction are stone in the common duct, carcinoma of the head of the pancreas, and pressure on the common duct from carcinoma metastases.

In case 7 the obstruction was incomplete, as bile was present in the stools. A normal diet was maintained and in the presence of bile in the intestinal tract there was sufficient prothrombin formation. The clotting time became disturbed only after operation, when the T-tube draining the common duct became blocked and actually a biliary fistula was created. Hawkins and Brinkhous[33] produced a hypoprothrombinæmia in bile-fistula dogs, and Greaves and Schmidt[34, 35] demonstrated a similar result in bile-fistula rats. The above case is of interest since it confirms the work of these investigators, demonstrating that hypoprothrombinæmia may result in the human subject from biliary fistula in the same manner that it has been produced in the experimental animal. It also accentuates the part that bile plays in the absorption of fat-soluble substances or vitamin K.

Another group of patients have shown normal clotting times in the presence of jaundice of the obstructive type. In all these patients there was no abnormal bleeding tendency at operation, suggesting that the prothrombin level was not markedly reduced. In this type of case, however, prophylactic therapy should be carried out, as bleeding at operation may be sufficient to reduce the prothrombin below the critical level where bleeding will occur. This was well demonstrated in Case 8. Pre-operative blood studies indicated normal prothrombin levels. Shortly after operation continuous bleeding occurred and this was controlled by blood transfusion followed by large doses of vitamin K concentrate. The clotting time returned to normal in 36 hours and was maintained at this level, with cessation of the bleeding.

The rôle of hepatic injury has been noted previously.[16] In no case was there excessive liver damage to impair the utilization of vitamin K in the formation of prothrombin.

Another factor which investigators have commented on is the occurrence of K-avitaminosis due to faulty diet. The tendency in the past to feed all patients with jaundice a low fat diet predisposes to a K deficiency. This may be ac-

centuated by the marked nausea and vomiting which so often accompanies gall-bladder disease.

In this short series too few cases have been studied to warrant any extended comment on dosage. It would seem that the larger the dosage employed, the quicker the return of the prothrombin level to normal, and, further, the earlier a prothrombin deficiency is detected, the less vitamin K is required for its control and the less danger of important loss of blood. The unitage system now used to indicate the vitamin K potency is somewhat complicated, as various investigators use the preventive or curative assay. In the preventive assay the material is given in the diet, and the individual dose for this reason is not susceptible of control. The curative method is more accurate, but different methods are used. Therefore, until more extensive comparative assays have been carried out, using an agreed standard, the relationship between the different units must be, at best, only approximate. Using the Dam unit as an approximate standard, we have obtained satisfactory results with 50,000 to 90,000 Dam units, and where massive dosage was required 200,000 to 250,000 units of vitamin K were given per day. One to three grams of bile salts per day seems adequate.

SUMMARY

Ten cases of obstructive jaundice are presented in which the plasma prothrombin levels were low and in which there was an abnormal tendency to bleed as indicated by the prolonged clotting times.

Administration of vitamin K and bile salts restores the clotting time to normal. One failure with no adequate explanation is recorded.

No abnormal bleeding followed operation in those treated with vitamin K and bile salts.

After operation there may be further disturbance in the plasma prothrombin, with an abnormal tendency to bleed, as illustrated by one case and prophylactic therapy is suggested as a safeguard.

Biliary fistula may result in a reduction of plasma prothrombin with a resulting abnormal tendency to bleed. This adds confirmation of the experimental work done with biliary-fistula dogs and rats.

It is suggested that the tendency to feed patients with jaundice a low fat diet predisposes to K-avitaminosis which may be accentuated further by the nausea and vomiting which so often accompanies obstructive jaundice.

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PATHOLOGY OF INSULIN SHOCK.—The author describes experiments on sixteen dogs. In those which died in insulin coma acute diffuse œdematous changes were found, not all of which were reversible. In some parts the neurones showed advanced necrosis with corresponding changes in the neuroglia and vessels. In dogs killed five to seventeen days after the last of a series of twenty-five to thirty shocks over forty to fifty-four days similar but less severe lesions were found. Certain suggestions as to the explanation of the therapeutic effect of insulin shock are made.—Accornero, F.: *Riv. di Patol. Nervosa e Mentale.*, 1939, **53**: 1. Abs. in *Brit. M. J.*