Bleeding from Occult Tumors during Anticoagulant Therapy

By Milton M. Michaels, M.D.

The common use of anticoagulant drugs in the treatment of thrombotic manifestations has increased the awareness of resulting complications, notably bleeding from the gastrointestinal and the genitourinary tracts. The incidence of such complications has been estimated between 2 and 19 per cent.\textsuperscript{1} Fatal hemorrhage in a series of 1,091 patients was 0.5 per cent.\textsuperscript{2, 3}

When a hemorrhage occurs, it is usually attributed to the anticoagulant. This causal relationship is strengthened by the observation that discontinuing the drug, or giving specific antagonists like vitamin K or protamine sulfate, usually results in rapid cessation of the bleeding. Therefore, in many instances no further investigation of the bleeding site is made.

Recently, the hospital charts of five patients who bled during anticoagulant therapy were reviewed. In each case, the bleeding was promptly controlled by specific therapy or by discontinuation of the anticoagulant. Further investigation revealed the presence of an unsuspected tumor. Brief summaries of each case are presented.

\textbf{Case Reports}

\textbf{Case 1}

A 59-year-old man was hospitalized for treatment of thrombophlebitis of the left great saphenous vein. Past medical history included a gastroenterostomy for a peptic ulcer 9 years ago. Physical examination was within normal limits except for tenderness above Poupart’s ligament and swelling and tenderness of the left thigh. Following therapy with intravenous heparin, swelling and pain in the involved extremity decreased.

On the fourth hospital day the patient complained of nausea and abdominal pain and passed two black stools. Lee-White clotting times, taken 4 hours after the heparin doses were consistently under 13 minutes and the prothrombin time was 28 per cent. Heparin was reduced and antacid therapy was started. An upper gastrointestinal series showed a soft-tissue mass in the stomach. At exploratory laparotomy a colloid adenocarcinoma was found in the stomach, duodenum, pancreas, and in many lymph nodes extending to the liver.

\textit{Comment}. An occult malignancy became manifest by gastrointestinal bleeding during heparin therapy. The well-known association of phlebitis and occult malignancy is apparent here, and the bleeding pinpointed the involved area.\textsuperscript{4, 5} The patient had no gastrointestinal symptoms until he received anticoagulants for several days. At no time was the clotting time outside the therapeutic range.

\textbf{Case 2}

A 56-year-old man was admitted to the hospital because of rectal bleeding. He had been on anticoagulant therapy (Warfarin) for several months because of myocardial infarction and peripheral circulatory insufficiency. He had no previous history of rectal bleeding, anemia, or weight loss. A sigmoidoscopic examination revealed an adenocarcinoma in the sigmoid colon. The hemoglobin was 7.7 Gm. per 100 ml., the hematocrit level was 22 per cent, and the prothrombin concentration (Quick) was 27 per cent.

\textbf{Case 3}

A 72-year-old man complaining of abdominal cramps showed T-wave abnormalities and a pattern of left ventricular hypertrophy. A diagnosis of abdominal angina was made and coumadin sodium (Warfarin) therapy was started. During the next 4 weeks the patient noted bright rectal bleeding in small amounts and constipation relieved by cathartics. Prothrombin times were within a therapeutic range.

A barium enema then revealed an annular carcinoma of the splenic flexure of the colon. Anti-coagulants were discontinued and a papillary adenocarcinoma of the colon was resected.

\textit{Comment}. The early abdominal cramps described by this patient were probably related to the tumor. Rectal bleeding was initially interpreted as being...
related to Warfarin therapy. No further studies were undertaken until more symptoms developed.

Case 4

A 71-year-old man was started on coumadin sodium (Warfarin) in July 1959 following an acute myocardial infarction. Prothrombin times, done at regular intervals, were reported as within the therapeutic range. The patient was hospitalized in April 1961 for epistaxis, bright rectal bleeding, and congestive heart failure. The prothrombin concentration on admission was less than 10 per cent. Intravenous vitamin K₁ was given followed by a prompt cessation in the bleeding. The hemoglobin was 14.4 Gm. per 100 ml and the hematocrit level 46 per cent. Because of the patient's cardiac status, no further evaluation of the rectal bleeding could be undertaken.

Four weeks later he was rehospitalized with bowel obstruction. A barium enema showed an annular carcinoma of the sigmoid colon. He was prepared for surgery but went into cardiac arrest during the induction of anesthesia and succumbed despite thoracotomy with cardiac massage.

Comment. This patient received Warfarin therapy for nearly 2 years without incident. As in case 3, the epistaxis and rectal bleeding could easily have been attributed to excessive anticoagulants, since both subsided promptly with administration of vitamin K. Unfortunately, the patient was too ill for studies when the rectal bleeding first occurred.

Case 5

A 71-year-old man was hospitalized with motor aphasia and partial paresis of the right upper extremity. Examination following stab wounds in 1957 revealed no pathology or evidence of intraperitoneal bleeding. The hemoglobin at that time was 12.5 Gm. per 100 ml and the hematocrit value was 42 per cent.

A right-sided hemiparesis and verbal aphasia recurred on the fifth hospital day. The diagnosis of thrombosis of the left middle cerebral artery was made, and anticoagulant therapy (Warfarin) was instituted.

Routine stool examinations were positive for occult blood and the hemoglobin dropped from 10.5 to 7.5 Gm. per 100 ml. A gastrointestinal series revealed a malignancy of the stomach. Anticoagulants were discontinued, and the patient was transfused. A gastroscopy was performed and necrotic tumor tissue observed but a biopsy specimen was unsatisfactory. Because of the patient's precarious state, an exploratory laparotomy was deferred.

Comment. At no time was the prothrombin time outside a therapeutic range. This patient was anemic on admission, probably due to occult rectal bleeding even before anticoagulant therapy.

Discussion

A review of the English literature reveals only five instances of occult malignancy presented as bleeding during anticoagulant therapy. Nichol²,³ cited a case of vaginal bleeding during treatment with anticoagulants for myocardial infarction. The bleeding was found to arise from an early carcinoma of the cervix. Stern and Dreskin¹ reported an instance of hemoptysis due to a bronchogenic carcinoma that developed during anticoagulant treatment for thrombophlebitis. Goodman⁶ described a case of recurrent phlebitis treated with intravenous Warfarin in which bleeding occurred when the prothrombin time was excessively long. An infiltrating carcinoma of the pancreas was ultimately found. As in case 1, this patient suffered from phlebitis, which has been noted with occult malignancy.⁴,⁵ Hemley et al.⁷ reported three patients who bled during anticoagulant therapy. Two of them were being treated for thrombophlebitis, the third for myocardial infarction. One of the patients with phlebitis developed hematuria due to papillary adenomas in a polycystic kidney; the other had gross rectal bleeding due to an adenocarcinoma of the descending colon. The third patient had hematuria, caused by a hypernephroma. In all three patients the prothrombin times were prolonged beyond the therapeutic range.

The probability of uncovering an occult malignancy in a patient with bleeding manifestations during anticoagulants is small. Since the chances of obtaining a cure of cancer depend in part upon early diagnosis, it behooves physicians to follow all possible leads. Such situations are clearly presented in the reported patients who developed bleeding while on anticoagulant therapy.

Summary

Five patients treated with anticoagulants for a variety of reasons developed gastrointestinal bleeding. Further diagnostic studies in each case uncovered a previously unsuspected tumor.
Acknowledgment

I wish to thank Dr. Jessica H. Lewis for reviewing this manuscript and for her helpful suggestions, and Drs. Albert Amshel, Leslie Morris, Sidney Rosenberg, Irving Stutz, and Marvin Silverblatt, for permitting me to use records of their patients for this article. Cases 1 to 4 are from the Montefiore Hospital, Pittsburgh, Pennsylvania; Case 5, Oakland V. A. Hospital, Pittsburgh, Pennsylvania.

References


What the next turning point of our understanding of disease may be is a matter for surmise and speculation. I would hazard the guess that the next interpretation of disease will in some way involve an increased emphasis on the ecological approach. Ecology is the branch of biology which deals with the mutual relations between organisms and their environment. The more we learn about living creatures, whether plant or animal, the more impressive becomes the evidence of the interrelatedness of living things. They obviously live on each other as predators or as parasites. Somewhat less obviously, they live with each other in varying degrees of mutual aid and dependence. For all its complexity, ecology provides a fascinating kind of understanding of what goes on.

Perhaps one of the first powerful results of interpreting disease as an ecologist would regard it would be a greater interest in convalescence and rehabilitation. Surely, it is no loss to medicine if the ecologist joins hands with the economist and the humanist in holding that the return to wage earning and independence forms part of the cure. Indeed, we are beginning to see rehabilitation as a growing fringe of Great Medicine.—ALAN GREGG, M.D. Challenges to Contemporary Medicine, New York, Columbia University Press, 1956, p. 38.
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Circulation. 1962;25:804-806
doi: 10.1161/01.CIR.25.5.804
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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