

Review

Bleeding during oral anticoagulant therapy

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It seems to be appropriate to recall that the use of prothrombin-depressing agents in man stems from the fact that Dicumarol produces a severe bleeding disorder in cattle.¹ The isolation of 3,3'-methylenebis (4-hydroxycoumarin) (Dicumarol) by Link and colleagues² in 1939, as the causative agent in Schofield's "sweet clover disease" ushered in the era of oral anticoagulant therapy. The fact that Quick already had devised a simplified method for detecting the coagulation defect induced by this agent and had noted that the associated hemorrhagic disorder could be related to the severity of this deficiency³ encouraged prompt trial of Dicumarol as an anti-thrombotic agent in man. After preliminary investigation in dogs,⁴ Meyer and associates⁵ studied responses in 50 patients and urged that the minimal effective dose be employed. Nevertheless, bleeding was frequent in early clinical trials with this drug.^{6,7} By 1949, Duff⁸ was able to find 21 reported fatalities from hemorrhage induced by Dicumarol, and added 2 cases to that number.

In spite of the accumulation of a vast experience with oral anticoagulant therapy, hemorrhage continues to complicate its usage. As emphasized by Peyman,⁹ the frequency of bleeding has probably di-

minished as familiarity with these agents has increased over the years; but even in the most recent reports, hemorrhage continues to be a common problem.¹⁰ Review of a number of studies on hospitalized patients¹¹⁻¹⁵ indicates that bleeding occurs in approximately 10 per cent of cases. Hemorrhage is even more common in ambulatory patients,^{9,16-18} affecting 1 of every 3 so treated in this country and England. However, these episodes are largely minor and fatalities are rare. The percentage of bleeding is higher among outpatients, primarily because the protracted nature of the treatment puts the subject at risk over a longer period of time, but also because the intensity of supervision by the physician is diminished. Diet, habits, consumption of drugs, general health, and blood prothrombin activity cannot be as carefully controlled as is possible during hospitalization.

Clinical picture

Newcomb and associates¹⁹ have emphasized the diffuse nature of bleeding produced by the indirect anticoagulants in contrast to the focal "blow-outs" observed in patients with hemophilia, whereas Owen²⁰ has been impressed by similarities between the bleeding of patients with

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Christmas disease and that of patients receiving anticoagulant therapy. In our experience, severe overdosage produces a diffuse hemorrhagic disorder dominated by hematuria, gastorintestinal bleeding, and wound oozing, but the most common single source of bleeding is the urinary tract. Hematuria was the primary clinical problem in approximately 40 per cent of 130 hemorrhagic episodes observed at the University of Michigan Medical Center from 1947 to 1960. The appearance of blood in the urine was usually heralded by unilateral, and sometimes bilateral, flank pain. Diagnostic problems occasionally ensued when pain preceded the detection of gross hemorrhage by as much as 12 hours, especially when the pain was atypical in location. The point of bleeding was often found to be in the lower urinary tract when hematuria occurred in the absence of flank pain. In recent years, reports of atypical sites of bleeding in the absence of a generalized hemorrhagic diathesis have appeared. Some of the critical areas affected have been the brain,²¹ wall of the bowel,²² ovary,²³ and adrenal glands.²⁴ These unusual types of hemorrhage are rare, and fortunately so, since they are frequently fatal.

Cause

Spontaneous hemorrhage occurs, in general, because of disturbances in platelet activity, plasma coagulation factors, or vascular integrity. It is well known that the coumarin and indanedione drugs impair coagulation, so that it is not surprising that bleeding during the administration of these agents has been attributed to this effect. In 1947, Allen and associates¹¹ reported that hemorrhage was rare when the "prothrombin activity" was above 10 per cent. It soon became apparent, however, that the coagulation defect produced by these agents was more complex than had originally been supposed. We now know that factors involved in both the first and second stages of coagulation are affected. Specifically, depressions of factors II (prothrombin),²⁵ VII (proconvertin),²⁶ IX (Christmas),²⁷ and X (Stuart-Prower)²⁸ have been demonstrated. Also, it has become apparent with widespread anticoagulant therapy that hemorrhage can

occur with prothrombin activity well above 10 per cent as determined by modifications of Quick's test. Because of this and the fact that determinations of "prothrombin time" do not reflect concentrations of all the factors influenced by oral anticoagulants, efforts have been made to correlate bleeding with levels of individual clotting factors. In fact, good correlations have been reported for factors II,²⁹ VII,³⁰ and IX.^{20,31} Most recently, Owen has placed heavy emphasis on the importance of factor X. Utilizing the "Thrombotest," which is particularly sensitive to depression of factor X during chronic anticoagulant therapy, he has reported the virtual elimination of bleeding in a large clinical experience by keeping values above 10 per cent.³² On the other hand, Rodman³³ could not confirm the value of assay of factor II, and Rapaport³⁴ demonstrated that levels of factor IX are never dangerously depressed when prothrombin concentration by the Quick method is 20 per cent or greater. More recently, Loeliger and associates³⁵ have found that factors II, VII, IX, and X are comparably depressed by the chronic administration of anticoagulants, and Baugh³⁶ has observed that levels of factors II, VII, IX, and X are no different in patients with prolonged prothrombin times who are bleeding than in subjects with similar prothrombin times who are not.

Bleeding with prothrombin activity at "safe" levels might be due to the additive effect of a latent disturbance in platelet or vascular function, since Jaques³⁷ has demonstrated in rats treated with Dicumarol that hemorrhage does not appear unless more than one hemostatic mechanism is impaired. The fact that petechiae occur^{38,39} in some patients receiving oral anticoagulants suggests that platelet-vascular factors may play a role in the production of bleeding during therapy. Spooner⁴⁰ found no decrease in the number of platelets during prolonged Dicumarol therapy in man, but she did demonstrate a decrease in the adhesiveness of platelets. Prolonged survival of platelets has been found by Murphy⁴¹ to accompany decreased stickiness of platelets during intensive anticoagulant therapy. There is no evidence, however, that these changes in platelet

function play a primary role in anticoagulant-induced hemorrhage. Peyman⁹ has reviewed the evidence indicating that hemorrhage during Dicumarol therapy is related to the production of a vascular defect; however, in his clinical study he found no convincing correlation between bleeding and tests of capillary fragility.

In our own experience,⁴² bleeding usually occurs in association with excessively depressed prothrombin activity as determined by the Quick test (values of 15 per cent or below), and previously unrecognized organic lesions are usually the cause of bleeding which starts at higher prothrombin levels. We have found that the major causes of bleeding during oral anticoagulant therapy lie in the realms of judgment on the part of the physician, laboratory technique, and the cooperation of the patient. These practical aspects of the use of prothrombin-depressing agents are carefully outlined by Duff.⁴³ Amplification of the problems encountered in one-stage prothrombin estimations, and particularly the pitfalls in the use of various thromboplastins and the construction of prothrombin-activity curves, can be found in the study of Rodman and associates.⁴⁴ Occasionally, bleeding occurs in association with sharp and unexpected declines in prothrombin activity, and patient, laboratory, and physician are all above reproach. Such complications are often related to additional medication which has increased the sensitivity to the oral anticoagulant. The list of drugs which can do this is lengthening steadily; it includes aspirin,⁴⁵ phenylbutazone,⁴⁶ tetracycline and streptomycin,⁴⁶ D-thyroxine,⁴⁷ ethyl chlorophenoxisobutyrate,⁴⁸ and methandrostenolone.⁴⁹

Treatment

Oil-soluble vitamin K₁ specifically counteracts the coagulation defect produced by coumarins and indanediones, and its availability has minimized the hazard of anticoagulant overdosage. The main problem with the use of this antidote is the selection of the dose to be given in specific circumstances. In early clinical trials with vitamin K₁, huge intravenous doses ranging from 500 to 1,000 mg. were used.^{50,51} It soon became apparent, however, that considerably smaller doses could be equally ef-

fective.⁵² Subsequently, various authorities^{43,53,54} have pointed out the potency of as little as 2.5 mg. of vitamin K₁ given intravenously or by mouth. The study of Rehbein and associates⁵² demonstrated quite well that even in dire circumstances the administration of more than 50 mg. intravenously was superfluous, if not hazardous. There are two reasons why it is desirable to administer the *minimum* effective dose. The one, which is well documented, is the development of resistance to subsequent oral anticoagulant therapy after excessive K₁.^{55,56} The other, which is not confirmed, is the development of "rebound" hypercoagulability, although the study of Sise⁵⁷ suggests that such a phenomenon may appear when prothrombin depression is reversed after a hemorrhagic episode. As opposed to the relatively inactive, water-soluble vitamin K preparations, vitamin K₁ emulsion given intravenously produces its beneficial effects in 4 to 8 hours.^{52,58} For this reason, it is rarely necessary to utilize any other form of therapy in the bleeding patient. If the situation is desperate, an immediate correction of the clotting-factor deficiencies can be obtained by infusing whole blood, plasma, lyophilized plasma, or a plasma fraction rich in clotting factors.⁵⁹ In general, the selection of the amount of K₁ to be used, and the choice of the route of administration is based on four factors: severity of hemorrhage, duration of prior treatment, severity of prothrombin depression, and the desirability of resuming therapy. Life-threatening bleeding demands the use of intravenous K₁ in maximal dosage (50 mg.). Mild hematuria in a patient during the first week of therapy responds to less K₁ than similar bleeding in the patient on long-term treatment. Hemorrhage with prothrombin time in excess of 60 seconds requires more K₁ than does the same problem occurring with less depression of prothrombin activity. If therapy is not to be continued after treatment of the bleeding episode, larger amounts of K₁ may be used than if the anticoagulant program is to be reinstated. In general, 15 to 25 mg. of K₁ is adequate to bring prothrombin activity back up to safe levels in patients with the usual mild anticoagulant-induced hemorrhage.

Prevention

A carefully selected, adequately informed, cooperative patient who is being followed closely by an experienced physician with the aid of properly trained laboratory personnel is the right combination for "safe" anticoagulant therapy. Most severe bleeding problems can be eliminated by adherence to that formula *if the therapeutic goal is kept within reasonable limits*. It must be recognized that Owren's P & P test and Thrombotest are, in general, more sensitive to the effects of coumarin drugs than the Quick test, so that a 10 to 20 per cent range with the former tests is equivalent to a 20 to 40 per cent range with the latter.^{54,48,60} This being the case, the danger level will depend on which test is being used. With the Thrombotest this level has been found to be at about 10 per cent activity. This suggests that the safe range with the Quick test lies above 20 per cent activity. It is doubtful whether the one test is superior to the other if this difference is kept in mind. In our experience, in the absence of focal vascular weakness, hemorrhage is rare at prothrombin concentrations greater than 20 per cent by the Quick test. Although there is some evidence from studies on hospitalized patients that more intensive therapy has a greater antithrombotic potential,^{11,61} a recent, limited study of this problem among ambulatory patients⁶² suggests that optimal results are obtained with Quick test values of 30 to 50 per cent. In the absence of further information relating efficacy of therapy to Quick test levels, it would appear that the lower end of the therapeutic range in outpatients followed with this test should not be under 20 per cent.

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