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# Surreptitious Ingestion of Oral Anticoagulants

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*Hypoprothrombinemia secondary to surreptitious ingestion of coumarin or indanedione anticoagulants may be a difficult diagnosis for the unsuspecting physician. Four such case reports are presented. The disease should be suspected if the prothrombin time is markedly elevated and the individual is associated with the medical profession or has had previous treatment with oral anticoagulants. The diagnosis is confirmed by finding a deficiency in Factors II (prothrombin), VII, IX, and X and the presence of the coumarin or indanedione anticoagulant in the blood. The motive generally is that of gaining attention rather than committing suicide. Liver disease, Vitamin K deficiency states and accidental ingestion of oral anticoagulants are the chief disorders to be considered in the differential diagnosis. Specific assays for the oral anticoagulants are indicated before assuming a rarer etiology for the hemorrhagic syndrome.*

The oral anticoagulants, coumarin and indanedione derivatives, are commonly used for the treatment of thromboembolic disease. Since 1951, occasional reports have appeared concerning surreptitious ingestion of oral anticoagulants as a cause of hypoprothrombinemia.[1-5] Recent discussion on this subject by Bowie and associates[2] and by O'Reilly and Aggeler[3] has emphasized certain diagnostic features. In addition, they made the observation that this particular form of malingering generally occurs in individuals closely associated with the medical profession or who have had previous treatment with oral anticoagulants.

Hypoprothrombinemia on the basis of surreptitious ingestion of coumarin or indanedione anticoagulants may present a difficult diagnostic and therapeutic problem for the unsuspecting physician. Our purpose is to emphasize the characteristic features, the management of the patient, the mechanism of competitive inhibition between oral anticoagulants and Vitamin K, and to discuss the psychodynamics of patient motivation.

## Materials and Methods

Coagulation studies of four patients are presented in Table I. The prothrombin time and plasma clotting time were measured by the methods described by Quick. The partial thromboplastin time was determined as described by Rodman, et al.[6] Prothrombin consumption was performed as described by Sussman, et al,[7] the two-stage prothrombin assay by the method of Ware and Seegers,[8] the thromboplastin generation test by the method of Biggs and Douglas,[9] and the prothrombin and proconvertin test by the method of Owren and Aas.[10] The concentration of warfarin in plasma was measured as described by O'Reilly, Aggeler and associates,[11]

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TABLE I

| | CASE I | CASE II | CASE III | CASE IV |
|---|---|---|---|---|
| Bleeding time (in minutes) | 4½ | | | |
| Lee-White clotting (time in minutes) | 11½ & 14 | 14 & 19 | 16½ & 18½ | 12½ & 16½ |
| Plasma clotting time (normal 80-120 sec.) | 150 | 190 | 300 | 165 |
| Prothrombin time (in seconds) | | | | |
| a) Control | 12 | 15 | 15 | 12 |
| b) Patient | 62 | 100 | 185 | 58 |
| Partial thromboplastin time (in seconds) | | | | |
| a) Control | 66 | 58 | | 58 |
| b) Patient | over 560 | no end pt. | | 270 |
| c) 1 part patient plasma plus 1 part normal plasma | 65 | 100 | | |
| Prothrombin consumption (normal greater than 25 sec.) | 145 | 93 | 95 | 42 |
| Two stage prothrombin assay (% of normal) | | | | |
| a) Control | 100 | 100 | 100 | 100 |
| b) Patient plasma with Factor V | 7 | 13 | 12 | 20 |
| c) Patient plasma without Factor V | 7 | 0 | | 19 |
| Factor II (% of normal) | 6.5 | 0 | 12 | 19 |
| P & P test of Owren for Factor VII & X (% of normal) | 8.5 | | | 5 |
| Russell viper venom & cephalin test for Factor X (% of normal) | 3 | | | 7 |
| Plasma Coumadin in mg./L. | 9.8 | | | 8.1 |

Coagulation studies in four cases of surreptitious ingestion of oral anticoagulants.

and the concentration of bishydroxycoumarin in plasma was measured as described by Axelrod, Cooper and Brodie.[12]

## Case Reports

*Case I*

The patient, aged 60 years, a white housewife and school teacher, was referred for evaluation of abnormal bleeding and refractory hypoprothrombinemia. In September, 1964, the patient developed thrombophlebitis following a fracture of the left leg. Sodium warfarin (Coumadin) therapy was initiated and continued until March, 1965. Recurrent thrombophlebitis necessitated reinstitution of warfarin in April, 1965. Subsequently, during an episode of abdominal pain and hematuria, the prothrombin time was found to

be 19%. It returned toward the normal range following daily intravenous injections of phytonadione (Aquamephyton). Later, however, the prothrombin time was again found to be elevated, but failed to return to normal with daily oral and weekly intravenous Vitamin K.

The patient was studied at a university hospital in another state. The only abnormalities found were a prothrombin time of 10%, a clotting time of 28 minutes, and a sulfobromophthalein retention of 12.5% in 45 minutes. The bleeding time was normal. An opinion was rendered that chronic liver disease accounted for her lowered prothrombin levels.

The patient continued to cause her family doctor serious concern. She appeared to respond only to intravenous Vitamin K and accordingly received phytonadione 40 mgs once a week. Without this therapy, hematuria and ecchymoses would occur. The patient then developed local skin reactions at the sites of the Vitamin K injections and her physician feared an imminent systemic reaction of the anaphylactoid type.

One year from the onset of her illness, she was admitted to the Henry Ford hospital on May 22, 1966. Her only medication at that time was 75 units of Lente insulin daily. She was a well-respected third grade school teacher, who had been seemingly happily married to a truant officer in the same school system for 37 years.

On examination, the patient was a very pleasant, slightly obese, motherly type of woman who appeared younger than her age. A fading ecchymosis was noted on the buttocks. Physical examination was otherwise unremarkable.

The routine laboratory examinations were normal, but the sulfobromophthalein test showed 9% retention in 45 minutes. The coagulation studies are recorded in Table I. There was a deficiency in Factors II (prothrombin), VII, X, and a probable deficiency in Factor IX (a test specifically for Factor IX was not performed). Significantly, the plasma warfarin level was found to be 9.8 mg/litre.

The diagnosis of coumarin toxicity was, therefore, established and her local physician was asked to contact her druggist. Her physician was surprised to find out that she had purchased refills of 5 mg warfarin tablets on at least five occasions during the previous year and as recently as two weeks before the present hospital admission. Consequently, her hospital room was searched in her absence, and warfarin 5 mgs was found wrapped in aluminum foil in her suitcase. These were left in place except for two tablets taken as "evidence."

On confrontation (by a psychiatrist), the patient denied self-medication, even though medicine had been found in her suitcase. However, several hours later, she stated to the medical resident, "I thought they were diet pills. I wasn't taking them intentionally." She then relinquished her supply of warfarin and vowed that she would never make the "mistake" again. The patient was permitted this face-saving explanation.

The blood warfarin levels subsequently decreased at a rate consistent with normal *in vivo* degradation of the drug. Phytonadione was administered in a dose of 5 mg orally twice a day. Two days later her prothrombin time was 15 seconds. She returned to her community where she became free of hemorrhagic phenomena.

*Case II*

The patient was a 30-year-old, single white female who was a registered nurse. Nine years previously, while in training, she developed idiopathic thrombocytopenic purpura. Symptoms were menorrhagia, metrorrhagia and easy bruisability. She received three whole blood transfusions and was treated with corticosteroids for one year. Symptoms subsided except for a moderate degree of menorrhagia.

In January, 1965, the patient sought medical attention for a recurrence of bruising and a worsening of menorrhagia. Between April and November, 1965, she was admitted to another hospital three times by her local physician. Her prothrombin time was as high as 102 seconds, but on each occasion the administration of intramuscular phytonadione was followed by a return of the prothrombin time to normal within 24 hours. In late November, 1965, she was referred to Henry Ford Hospital for investigation of possible liver disease or malabsorption of Vitamin K. She had always been obese, weighing 250 pounds ten years previously and 290 pounds on admission. She had twice made half-hearted attempts to reduce, but stated that now she did not really care.

On physical examination, in addition to marked obesity, several large ecchymoses were seen on the extremities and abdomen. The routine laboratory values and liver function profile were normal. However, the prothrombin time was 54 seconds the night of admission, 103 seconds the following day and reached a peak of 227 seconds on the fourth day of hospitalization. During this time she was given oral phytonadione 5 mg

three times a day. Phytonadione 72 mg was then given intravenously. The prothrombin time was 134 seconds just prior to giving the intravenous Vitamin K, and did not change significantly over the following days. The coagulation studies are recorded in Table I. Direct determination of the presence of an oral anticoagulant in the blood or urine was not performed.

The failure to observe a favorable response of the prothrombin time to administered Vitamin K was interpreted as indirect evidence that the patient had taken a massive dose of a coumarin drug just before her admission to the hospital. It was also likely that she was continuing to consume the drug while under our observation. The patient hotly denied this on confrontation. Nonetheless, she was informed that she could keep from getting into difficulty by making certain that she avoided ingestion of this type of drug. Her cryptic reply was, "Well, that is easier said than done." Following discharge from the hospital she was admitted to another hospital two months later with the same problem, and eventually underwent a hysterectomy.

*Case III*

The patient, aged 37 years, a single female housekeeper, was admitted July 23, 1958, with menorrhagia, melena, weakness, epistaxis, ecchymoses, and sore throat. She was acutely ill with marked pallor, a large hematoma in the pharynx, tender cervical and inguinal lymphadenopathy, diffuse abdominal tenderness and guarding, and ecchymoses confined mainly to the legs. The admission laboratory data included a hemoglobin of 5.0 gm/100 ml and a platelet count of 175,-000/ cu mm. The prothrombin time was 185 seconds (control 15 seconds). Subsequent coagulation studies are shown in Table I.

Interrogation of the elderly couple for whom the patient was a housekeeper, revealed that the man was receiving phenprocoumon (Marcumar) for the treatment of arteriosclerotic heart disease. When asked to check his anticoagulant supply, he noted that much of his phenprocoumon was missing. Phytonadione 50 mg was given intravenously to the patient as well as several units of whole blood. Within 24 hours the prothrombin time was 17 seconds (control 15 seconds). Subsequently, she admitted ingesting the anticoagulant. In this particular patient, this action was believed possibly to have represented an attempt to commit suicide.

*Case IV*

A white female student nurse, age 20 years, was admitted to Henry Ford Hospital March, 1968, with hematuria. The hematuria began three months earlier and initially cleared after treatment with sulfamethoxazole. Subsequently, the hematuria recurred and was associated with mild dysuria and frequency. Urine culture, excretory urogram, and cystoscopy were normal. Menstrual flow just prior to admission was unusually heavy. Because coagulation studies were suggestive of ingestion of oral anticoagulants, the patient was admitted to the hospital for further clinical and psychiatric investigation.

Her past history revealed symptomatology of recurrent "cystitis" since childhood. Her mother stated that her daughter always had a "weak bladder" and frequently sought medical care. Her local physician believed her symptomatology to be "functional" and warned against frequent medical contacts. Repeat urologic examinations over the years failed to reveal objective evidence to support her complaints except for two positive urine cultures which had been obtained 10 months and 26 months prior to this admission. The patient was considered to be an excellent student nurse who was due to graduate in three months. She was shy and rarely accepted dates.

Physical examination was unremarkable except for several ecchymoses on the arms and legs. Laboratory studies were normal except for a prothrombin time of 58 seconds. Coagulation studies are shown in Table I. The plasma warfarin level was 8.1 mg/litre.

A search of the patient, her hospital room, and her nursing school quarters failed to reveal warfarin. When confronted with our knowledge of her warfarin ingestion, the patient initially denied this and failed to show any emotional response. Three days later the patient confessed to warfarin ingestion. After discharge from the hospital she was to be followed by a psychiatrist with regard to emotional factors.

## Discussion

Hypoprothrombinemia is the result of a deficiency of one or more of those factors involved in the one-stage prothrombin time. These are Factors II (prothrombin), V, VII, and X. However Coumarin and the indanedione anticoagulants depress Factors II, VII, IX, and X and differ from one another only in their duration of action. Factor

VII is depressed most rapidly, followed in 24 to 48 hours by depression of Factors II, IX, and X. The action of these drugs occurs in the liver where they competitively interfere with Vitamin K synthesis, which thereby blocks the latter's contribution of a common protein precursor for the synthesis of Factors II, VII, IX, and X. In gross overdosage with coumarin, massive doses of Vitamin K cannot restore the coagulation defect, suggesting that the relationship cannot be regarded as a simple competitive system.

Administration of Vitamin K does not alter the rate of disappearance of coumarin from the blood stream, although the prothrombin time may return to normal. This observation also emphasizes the competitive inhibition of coumarin by Vitamin K, the excess Vitamin K permitting normal synthesis of the deficient factors. Findings in our first case demonstrate this point. In Figure I, it is noted that two days following discontinuation of the warfarin (Coumadin), the plasma warfarin was at an elevated level, but the prothrombin time was almost normal. When a patient has ingested a large amount of

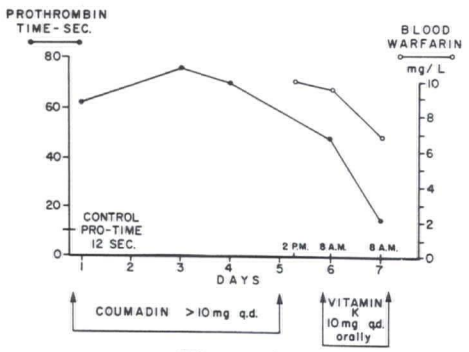


Figure 1

Degradation curve for plasma warfarin demonstrating practically normal prothrombin time on the seventh day while plasma warfarin is still markedly elevated.

oral anticoagulant, 50-100 mgs of Vitamin K intravenously daily for several days is required to correct the prothrombin time. The patient in our second case was thought to have ingested such a large amount of an oral anticoagulant that 75 mgm of Vitamin K was not sufficient to influence the prothrombin time.

A related consideration requires emphasis. The coumarin and indanedione drugs, though measurably present in the plasma, are not circulating anticoagulants since they exert their activity only in the liver and have no effect on coagulation *in vitro*. True circulating anticoagulants either block reactions between clotting factors (inhibitors) or destroy factors (inactivators). A screening test for circulating anticoagulants may be performed by adding one part normal plasma to one part patient's plasma and observing the effect on the plasma clotting time or partial thromboplastin time. If a circulating anticoagulant is present, the coagulation defect will persist. In our first two cases, the addition of normal plasma largely corrected the partial thromboplastin time, indicating that a true circulating anticoagulant was not present.

### Differential Diagnosis

Congenital deficiency of Factors II, V, VII, or X are rare. Acquired hypoprothrombinemia occurs primarily as a result of (1) liver disease, (2) Vitamin K deficiency, or (3) ingestion of an oral anticoagulant.

Parenchymal liver disease produces deficiences of the Vitamin K - dependent clotting factors, but in addition, Factor V is often depressed. Sherlock et al[13] found that the extent of par-

enchymal liver damage could be adequately assessed by the prothrombin time, bilirubin, serum albumin, and the clinical picture. Pertinently, it was noted that their patients with known severe liver disease, who had a prothrombin time of 1.5 times normal or longer, not correctable by parenteral Vitamin K therapy, died during that hospital stay. Therefore, a very long prothrombin time as an isolated finding will tend to eliminate parenchymal liver disease from the differential diagnosis. Furthermore, in parenchymal liver disease there is little or no response to Vitamin K parenterally. A good response to parenteral Vitamin K is generally observed within 24hours in Vitamin K deficiency due to other causes.

Dietary Vitamin K deficiency occurs as part of a complex of deficiencies in generalized malnutrition. Deficiency of Vitamin K also occurs when bile fails to reach the intestine (common bile duct obstruction or fistula), if intestinal transit is increased (prolonged diarrhea), and if the absorptive function of the intestinal mucosa is impaired, as in sprue. In addition, prolonged treatment with certain antimicrobial drugs may result in a lack of Vitamin K-producing bacteria in the gut with consequent Vitamin K deficiency.

Accidental ingestion of anticoagulants may occur, producing a marked elevation of the prothrombin time. This can be confirmed by examining all medications being taken by the patient. In recent months we have encountered two patients who received oral anticoagulants by accident.[14] In each instance a severe hemorrhagic disorder resulted. A serum assay for an oral anticoagulant should be obtained when a markedly prolonged prothrombin time is unexpectedly encountered.

Drugs which have a similar but weaker effect than coumarin on clotting factors include salicylates, phenylbutazone, quinidine[14] and heparin. Several other drugs, although having no anticoagulant activity themselves, potentiate the action of the oral anticoagulants. Phenyramidol hydrochloride and clofibrate are such drugs.[15]

In the presence of a naturally occurring circulating anticoagulant the prothrombin time is prolonged in almost every instance, sometimes to a marked degree. This is most commonly encountered in association with systemic lupus erythematosus, and can be recognized by failure to correct with added normal plasma (*vide supra*). Intravascular coagulation and fibrinolysis deplete the blood of prothrombin but the associated depression of Factors V and VIII, and generally of platelets, removes consideration of coumarin drug ingestion as a cause.

### Psycho-Sociological Considerations

Relatively little is noted in the literature as to the psychodynamics of the patients with surreptitious ingestion of coumarin. These individuals usually appear to be intelligent and of average or above average socio-economic status. Previous experience with anticoagulants or some association with the medical profession is common in this group. Of the 36 cases (including our own) that appear in the literature, 80% are female and 60% of all cases are registered nurses. Suspect individuals are those who have ready access to the drugs, such as pharmacists, nurses, doctors and orderlies.

None of these 36 patients underwent extensive psychiatric evaluation. Attempts at psychiatric evaluations were made in two of our patients, but in both instances the patient viewed the psychiatrist as a detective, making it impossible to interview the patient in depth. Our fourth case, the student nurse, was of particular interest. This patient had focused the attention of her parents and doctors on symptoms from her urinary tract since childhood. One doctor referred to her symptoms as being "ninety per cent functional." The patient may well have felt that she was being ignored by her doctor and succeeded in startling him when she presented with hematuria.

There can be considerable speculation as to why an individual would surreptitiously ingest a relatively dangerous drug. It would appear that the motive for bringing this bleeding disorder upon one's self would be to gain greater attention from family, friends, doctors, and the community. An underlying neurotic or psychotic process is likely. These patients could be considered to have a form of malingering. Our third patient was presumably attempting suicide and, if so, was not truly malingering.

The suggested approach is to confront the patient in a non-judgmental fashion. It is the physician's responsibility to try to understand the patient's difficulty and to communicate to the patient his wish to help. The physician must inquire into the stresses that led the patient into this unusual behavior. Frequently, if not usually, the patient refuses the invitation to explore the situation further because of his resentment and guilt.[16] However, the groundwork may be laid for the patient subsequently to come to grips with his basic problems in a more constructive fashion. On the other hand, the patient may continue the surreptitious ingestion of anticoagulants or he may substitute another drug with possible greater hazard to health.

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