PROTHROMBIN PATTERN OVER THE 24 HOURS IN PATIENTS RECEIVING ORAL ANTICOAGULANTS

BY

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Much is known about daily prothrombin concentration in patients receiving oral anticoagulants, but we can find no published observations on prothrombin levels at shorter intervals. The purpose of this investigation was to determine the variation of prothrombin concentrations throughout the 24 hours.

Methods

Nineteen patients were studied (17 males and 2 females); 9 had myocardial infarcts, 4 coronary insufficiency, 3 venous thromboses in the leg, and 3 pulmonary embolisms. Ten patients received phenindione ("dindevan") and 9 ethyl biscoumacetate ("tromexan"). All prothrombin estimations were made by one of us (E. G. W.), using Quick's one-stage method. The anticoagulant was given as a single dose at 6 p.m., and blood specimens were taken two-hourly from 6 p.m. until 6 p.m. the following day. The interval between the start of treatment and the 24-hour test period varied from patient to patient.

Results

The two-hourly prothrombin concentrations are expressed as a percentage of normal in Tables I and II. The mean

prothrombin level at each two-hourly interval is shown separately for ethyl biscoumacetate and phenindione in Fig. 1. Patients on ethyl biscoumacetate had an average prothrombin level about 10% higher than those on phenindione therapy, a purely adventitious difference which persisted throughout the experiment. Nevertheless, the overall effect is similar for both preparations, showing a small initial rise followed by a gradual and progressive decline until about noon, when the level begins again to increase. The trend probably represents a progressive depression of prothrombin level by the anticoagulant until its effect begins to wear off. We do not know whether the prothrombin level has a diurnal rhythm in a normal individual, but it is unlikely that a picture which conforms

FIG. 1.—Mean prothrombin level. Abscissa: hours after administration of anticoagulant. Ordinate: per cent. normal prothrombin.

TABLE I.—Phenindione. Two-hourly Prothrombin Concentrations Expressed as Percentage of Normal

Case	6 p.m.	8 p.m.	10 p.m.	12 p.m.	2 a.m.	4 a.m.	6 a.m.	8 a.m.	10 a.m.	Noon	2 p.m.	4 p.m.	6 p.m.
1. Myocardial infarct. . .	29	29	32	32	27	27	26	23	21	21	26	25	26
2. " " " " " " " " " "	28	26	26	24	25	24	24	24	24	21	24	22	—
3. " " " " " " " " " "	34	34	31	34	31	28	28	28	31	28	29	34	34
4. Vein thrombosis " " " " " " " " " "	23	22	22	21	28	26	21	22	20	18	17	18	17
5. " " " " " " " " " "	18	20	22	20	20	18	20	20	19	21	20	20	20
6. Pulmonary embolus. . .	24	25	28	28	20	20	15	18	15	15	15	15	18
7. Coronary insufficiency	20	23	25	27	37	25	26	31	24	23	22	22	30
8. Myocardial infarct " " " " " " " " " "	40	40	38	45	38	40	40	30	30	26	32	32	28
9. " " " " " " " " " "	42	38	42	36	33	33	36	34	38	34	36	38	34
10. " " " " " " " " " "	40	45	45	34	40	36	34	34	31	31	34	34	—

Optimum range
10-30%

TABLE II.—Ethyl Biscoumacetate. Two-hourly Prothrombin Concentrations Expressed as Percentage of Normal

Case	6 p.m.	8 p.m.	10 p.m.	12 p.m.	2 a.m.	4 a.m.	6 a.m.	8 a.m.	10 a.m.	Noon	2 p.m.	4 p.m.	6 p.m.
1. Coronary insufficiency	55	50	55	50	50	55	36	40	40	42	40	40	40
2. " " " " " " " " " "	36	45	40	36	24	32	29	34	27	29	31	30	36
3. Myocardial infarct " " " " " " " " " "	12	12	16	15	16	14	14	14	14	14	15	14	17
4. Coronary insufficiency	31	40	28	32	47	52	56	47	38	30	25	40	40
5. Myocardial infarct " " " " " " " " " "	54	50	30	40	50	50	48	48	31	48	43	48	50
6. Pulmonary embolism. . .	45	42	45	34	48	58	40	40	42	40	44	40	38
7. " " " " " " " " " "	37	36	37	37	31	38	32	28	23	27	24	39	34
8. Vein thrombosis " " " " " " " " " "	29	29	36	34	31	29	29	28	25	23	23	26	28
9. Myocardial infarct " " " " " " " " " "	31	30	36	36	34	36	36	31	28	27	27	27	26

Optimum range
10-30%

so well to expectation would also correspond so closely to a natural rhythm, or would show so wide a range of variation.

On average the ethyl biscoumacetate group showed a wider variation of prothrombin over the 24 hours than the phenindione group, four patients treated with ethyl biscoumacetate having a range of variation greater than 20%, whilst the greatest range among patients on phenindione was 19%. The variability of the two groups is compared in Fig. 2, where the standard deviation of the readings obtained at each interval of two hours is plotted against time. As in Fig. 1, the ethyl biscoumacetate figures are drawn both including and excluding one case with an unusually low prothrombin level. The only noticeable difference between

FIG. 2.—Standard deviation. Abscissa: hours after administration of anticoagulant. Ordinate: per cent. normal prothrombin.

phenindione and ethyl biscoumacetate is a vertical shift of the curve; the general shape remains unchanged, and each patient shows broadly the pattern of response exhibited in the mean curves of Fig. 1. The ethyl biscoumacetate group does not differ greatly when the aberrant case is excluded.

When allowances are made for differences between individuals and differences in times of day, the residual variation—attributable to uncontrolled factors and errors of determination—is small, amounting to a standard deviation of just over 3% in the phenindione group and about 5½% in the ethyl biscoumacetate group.

Conclusions

An experiment of this kind is laborious and involves considerable inconvenience to the patient. The number of observations has therefore been limited, but the following conclusions may be drawn.

1. Anticoagulants of the ethyl biscoumacetate and phenindione type are effective when given in a single daily dose as soon as the patient is considered to be stabilized.
2. The prothrombin concentration remains at a relatively high level for 8 to 10 hours after administration of the anticoagulant, and falls progressively to its lowest level after about 18 hours.
3. Blood for prothrombin estimations should be withdrawn from any individual patient at approximately the same time of day.
4. Although our investigation has shown a difference in response to the two anticoagulants, our observations are not sufficient to allow an appraisal of their relative merits.

A CASE OF ACUTE PHLEGMONOUS CAECITIS WITH PERFORATION

BY

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Acute phlegmonous caecitis is still regarded as a rare disease, and the condition is not described in standard textbooks. Only approximately 40 cases have so far been reported in the medical press, and most reports originate from practitioners in the U.S.A. The first case of phlegmon of the large intestine was reported by Goldschmidt (1887). Later on Hallopeau and Monod (1919) described the condition under the heading, "Gangrène massive du Caecum." Hagler (1920) reported a case of a dissecting interstitial abscess of the caecal wall. A case of ruptured gangrenous caecum in a child of 8 was reported by Rose (1932). Cox (1944) published two cases of acute gangrene of the caecum. Spivack and Busch (1943) reported two further cases of phlegmonous caecitis. A case of the same condition in a man aged 35 is described by Meyer and Disch (1945); further cases have been reported by McHardy and Browne (1946), Bulmer (1947), Riker, Gilchrist, and David (1949), and Nardell (1949); and Tagart (1953) surveys 21 cases reported during the last 25 years with three further cases.

Pathology

Two types of phlegmonous caecitis have been described by most authors, circumscribed and diffuse. A normal appendix is found in all cases, except when the appendix has become inflamed by contiguity. There are, however, distinct signs of an inflammatory lesion in the right iliac fossa, and, according to the type of the disease, there may be a well-defined thickening of the caecal wall or diffuse induration of the entire caecum. The affected area shows signs of acute inflammation, and ulcers penetrating as far as the serous coat have also been described. Gangrene with perforation and general peritonitis occurred in the case to be reported. On many occasions the lesion has been mistaken for carcinoma. The microscopical picture consists of infiltration by polymorphonuclear leucocytes in the submucosa and to a less extent in the subserosa, muscularis, and mucosa. According to Spivack and Busch the lesion is said to begin as a cellulitis of the submucosa. Streptococci and staphylococci, but also *Bact. coli* and pneumococci, have been isolated, and most authors agree that bacterial invasion of the submucosa following trauma by hard faeces, foreign bodies, fruit stones, or parasites is the most likely cause of phlegmonous caecitis. As additional causes anatomical abnormalities such as a mobile caecum with stasis have been suggested. The possibility of a haematogenous portal of entry has been stressed by Spivack and Busch.

Clinical Features

Most cases of acute phlegmonous caecitis have been diagnosed either as acute appendicitis or as appendix abscess. Most authors agree that a mass appearing in the right iliac fossa early, even in the first 48 hours, may be indicative of the condition. The disease has occurred in children and adults, and it is no more frequent in males than in females. The history is usually short. The diagnosis in the case reported below was made difficult by the fact that the patient was admitted in a diabetic coma. A precise history could not be obtained, and the symptoms of advanced peritonitis became obvious only when the patient started to regain consciousness. A mass could not be palpated.