Effect of Digitalis on the Clotting of the Blood in Normal Subjects and in Patients with Congestive Heart Failure

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Two groups of subjects were studied in order to evaluate the effect of digitalis on the coagulation of blood. One consisted of hospital patients in congestive heart failure, the other of normal interns. Control determinations were made of clotting and prothrombin times. Various preparations of digitalis were then administered in therapeutic doses. During administration, serial determinations were made of clotting and prothrombin times. The results were tabulated and the effect of digitalis appraised.

INTEREST in the intravascular clotting of the blood has been stimulated by the introduction into clinical usage of the anticoagulants, heparin and dicumarol. They have proved of particular value in the treatment in various disorders of the cardiovascular system in which thrombosis and embolism are so often disturbing complications. It is in this very group of diseases that digitalis is commonly employed as a therapeutic agent; and it has been claimed by various workers that this drug exerts an action in the body which favors coagulation of the blood. If true, it might be advisable to employ digitalis with caution, or perhaps avoid its use in those conditions in which it is most effective. In order to obtain further information on this point the present study was undertaken.

Tanaka[1] first drew attention to the thromboplastic action of the digitalis group of drugs, stating that strophanthin shortened the clotting time of the blood. Werch[2] described a 25 per cent decrease in the clotting time in rabbits following adequate digitalization. Decourt and Barbato[3] reported a decrease in blood coagulation time in 32 digitalized patients. Massie, Stillerman, Wright, and Minnich[4] determined clotting times before and after digitalization in 24 patients and found an average decrease of 3.3 minutes.

On the other hand, Ramsey, Pinschmidt, and Haag[5] found no change in the blood coagulation time of dogs following a single dose of digitalis.

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Sokoloff and Ferrer[6] found no significant change in the blood clotting time of 10 patients in congestive failure following the administration of digitalis.

In 1943, Macht[7] reported that cats previously heparinized were much less susceptible to toxic doses of digitalis than were untreated animals. In his opinion this may have been due to counteraction of a thromboplastic function of the digitalis glycosides. During the same year de Takats[8] described a heparin tolerance test and in subsequent work with Trump and Gilbert[9] found that digitalized animals were unusually insensitive to heparin administration. Moses,[10] using a similar test, found no decrease in the clotting time and no change in the response to heparin following the intravenous injection of digitalis.

Poindexter and Meyers[11] observed no alteration in the prothrombin times following adequate doses of digitalis.

MATERIAL

Two groups of subjects were studied before and after digitalization: (1) 17 cardiac patients in congestive heart failure; (2) 21 normal hospital interns and medical students. A third group of 14 hospital patients were used as controls. The latter were hospitalized for various reasons but none had liver disease or any disorder of the blood-forming organs. None received any medication which might affect blood clotting, nor was any given digitalis. Coagulation times were determined by two methods, the Lee-White and the Leifer, before digitalization and daily for a period of five days following digitalis therapy. Prothrombin times were determined at the same time on both undiluted plasma and plasma diluted eight times with normal salt solution (12.5 per cent plasma). Since the cardiac patients were all in moderate or severe congestive failure, it was

considered undesirable to make more than one observation before digitalis was given in order to avoid delay in carrying out treatment.

Of the patients in congestive failure, 14 were digitalized with the purified glycoside, digitoxin; these received 1.5 mg. to 2.4 mg. in five days. The average dose was 2.1 milligrams. The remaining 3 patients were digitalized with lanatoside C. Two of these received 1.6 mg. initially by intravenous injection and during the subsequent four days were given 1.2 mg. digitoxin by mouth. The third patient received 1.2 mg. lanatoside C intravenously and a total of 5 U.S.P. XII units of digitalis leaf by mouth during the next five days. In all patients the desired therapeutic response was obtained clinically.

Of the group of normal subjects who were digitalized, 4 received digitalis leaf. The total dosage for five days ranged from 18 to 20 U.S.P. XII units, the average dose being 19.8 units. The remaining 17 subjects received the glycoside, digitoxin. The total dosage for five days ranged from 1.8 mg. to 3.0 mg., the average dosage being 2.0 milligrams. In this group the clinical therapeutic effect of digitalis was, of course, not obtained. However, it should be noted that two of the subjects experienced minor toxic symptoms. One of these (H.A.) received 21 U.S.P. XII units of digitalis leaf and the other (R.C.) 3 mg. digitoxin. In the first patient anorexia and a few premature ventricular beats were noted. In the second a bigeminal pulse appeared and persisted for four days.

Methods

No subjects were included in the study who did not have easily accessible veins, and in all instances in which there was any difficulty with the venipuncture the specimen was discarded. Blood was removed with a 19-gage needle, the tourniquet being released as soon as the vein was entered.

Clotting Times. (A) Lee-White Method: The technic used was a slight modification of that described by Lee and White.[12] Three 75- by 10-mm. test tubes were placed in a warm water bath, the temperature of which was maintained between 36 and 39 Centigrade. One cubic centimeter of venous blood was placed carefully into each of the tubes. At the end of three minutes the first tube was tilted to the horizontal. This procedure was repeated every thirty seconds until the blood was seen to clot. The second tube was then similarly tilted and finally the third. The clotting time was considered to be the number of minutes which had passed when the blood in the third tube failed to flow down the side. To time the experiment the stop watch was arbitrarily started when one-half the total volume of the desired blood had been drawn into the syringe. All test tubes were cleansed daily with soap and water, potassium dichromate and concentrated sulfuric acid, and were rinsed with distilled water and oven-dried.

(B) Leifer Method[13]: Ten 75- by 10-mm. test tubes were placed in a warm water bath with the temperature maintained between 36 and 39 C. To each of these tubes was gently added 0.5 cc. of the subject's blood. The stopwatch was started as described above. At the end of the third minute the first tube was removed from the water bath, corked, rapidly inverted, and placed in a test tube rack while still inverted. At the end of each successive minute another tube was similarly inverted until all ten tubes had been removed from the bath. The end point was considered to be the time represented by that tube in which there first appeared a definite film of clot which remained at the bottom of the tube following inversion.

Prothrombin Times. These were determined by a slight modification of the Link-Shapiro adaptation of Quick's method.[14] The times are expressed in seconds. Into a chemically clean and oven-dried test tube was placed 0.01 gram potassium oxalate. To this were added 5.0 cc. of the subject's blood. The oxalated blood was centrifuged, and the plasma decanted and placed in a water bath maintained at 36 to 39 C. Fifty milligrams of desiccated rabbit lung* were diluted with 2.5 cc. of normal saline. This mixture was stirred vigorously for ten minutes in a water bath at 54 to 58 C. It was then cooled to 25 C. and 2.5 cc. of 0.025 molar calcium chloride were added. The resulting mixture was stirred for four minutes, centrifuged, and the supernatant fluid decanted. Two-tenths cubic centimeter of this solution was then placed in a 75- by 10-mm. test tube in a warm water bath (36 to 39 C.). When the calcium chloride-thromboplastin mixture had reached the temperature of the bath, 0.1 cc. of plasma was added. The mixture was vigorously stirred with a wire loop. The time was

* Prepared by the Maltine Company, New York, N. Y.

measured from the moment the first drop of plasma came into contact with the calcium chloride-thromboplastin mixture until a firm clot formed across the loop.

An identical procedure was carried out on both undiluted and 12.5 per cent plasma. In the latter case a normal solution of saline was used to dilute the plasma 1 to 8. A normal control blood was drawn each day within one hour of the time blood was obtained from the subject studied. Duplicate determinations were performed on each sample of the subject and the control blood throughout the study. Each prothrombin time listed in the tables represents the average of two determinations.

Results

Clotting Times. Using the Lee-White method, the average coagulation time of normal controls, including both the group of 13 undigitalized hospital patients and the group of 21 normal interns, before digitalization was 11.6 minutes. The overall range included the extremes of 8.5 minutes and 19.0 minutes. With the Leifer method the average time for the same group was 6.2 minutes with a range of 4 to 10 minutes. There was found to be a considerable degree of variation of coagulation times between individuals. However, individual subjects remained fairly constant throughout the study. Frequent determinations revealed that those subjects with somewhat longer clotting times tended to retain them from day to day. The same was true of those subjects with the shorter times.

In the group of patients in congestive failure the average coagulation time before digitalization was 11.9 minutes by the Lee-White method. Following digitalis the average time was 11.1 minutes, the average change being −0.8 minutes or −7 per cent. By the Leifer method the average clotting times before and after digitalization were 6.1 minutes and 6.0 minutes respectively, with an average change of −0.1 minutes or −2 per cent.

In the group of normal subjects who were digitalized, the average coagulation times with the Lee-White method were 12.1 minutes before and 12.3 minutes following digitalization, with an average change of +0.2 minutes or +2 per cent. The average time with the Leifer method was found to be the same before and after digitalization, namely 6.6 minutes.

In the patients in the control group, who received no digitalis, the average time by the Lee-White method was 10.7 minutes at the start and 11.0 minutes at the end of the study, a change of +0.3 minutes or +3 per cent. With the Leifer method the corresponding times were 5.6 minutes and 6.3 minutes respectively; the change was +0.7 minutes or +13 per cent.

From the data in tables 1, 2, and 3, it will be noted that some individuals showed slight shortening of the clotting times while others showed prolongation. It will be further noted that the changes in the clotting times were not always in the same direction by the two methods used. There was no significant difference in the response of the coagulation time to digitalis between patients in congestive failure and normal individuals. The degree of change noted in these two groups was of no greater magnitude than that noted in members of the control group who received no digitalis. Although considerable variation was found in clotting times when comparing individuals, the average times in all groups were of a similar degree of magnitude, and the average change following digitalization was small and statistically insignificant. There was very little change in the daily averages of the clotting times throughout the study.

Prothrombin Times. Using undiluted plasma the average prothrombin times of normal controls, including both the members of the group of undigitalized hospital patients and those of the group of normal interns, before digitalization was 13.34 seconds. The extremes were 11.9 seconds and 17.8 seconds. All but one determination on one subject fell within the range of 13.5 seconds ±1.6 seconds.

In the case of 12.5 per cent plasma the average prothrombin time of the same group of normals was 31.0 seconds with an over-all range of 25.5 seconds to 42.5 seconds. With the diluted plasma the range was found to be quite wide and the end point less reliable.

In the group with congestive failure the average times in seconds, using 100 per cent plasma, were 14.6 before and 13.8 after digitalization,

TABLE 1.—*Patients in Congestive Heart Failure before and after Digitalization*

Patient No.	Age (years)	Diagnosis	Total Digitalis in Five Days	Clotting Time of Blood (Minutes)						Prothrombin Time of Plasma (Seconds)					
				Lee-White Method			Leifer Method			Undiluted Plasma			2.15% Plasma		
				Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change
1	56	Coronary sclerosis	1.7 mg. digitoxin	8.5	10.0	+1.5	4.0	5.0	+1.0	13.1	11.2	−1.9	28.1	26.8	−1.3
2	82	Hypertensive cardiovascular disease	2.2 mg. digitoxin	10.0	9.0	−1.0	5.0	6.0	+1.0	13.2	14.1	+0.9	35.0	47.0	+12.0
3	56	Hypertensive cardiovascular disease	1.6 mg. lanatoside C 1.2 mg. digitoxin	8.5	8.0	−0.5	4.0	5.0	+1.0	13.7	13.6	−0.1	32.8	21.8	−11.0
4	52	Myocardial infarction	1.8 mg. digitoxin	8.5	10.0	+1.5	5.0	4.0	−1.0	13.4	13.0	−0.4	33.3	25.2	−8.1
5	65	Coronary sclerosis	1.5 mg. digitoxin	9.5	11.5	+2.0	5.0	5.0	0.0	13.8	13.2	−0.6	33.3	33.1	− 0.2
6	65	Cor pulmonale	2.3 mg. digitoxin	9.0	8.5	−0.5	5.0	5.0	0.0	15.7	13.1	−2.6	27.0	25.3	−1.7
7	64	Cor pulmonale	2.4 mg. digitoxin	15.0	9.0	−6.0	9.0	6.0	−3.0	17.9	14.4	−3.5	55.5	32.2	−23.3
8	56	Coronary sclerosis	1.2 mg. lanatoside C 4 U digitalis	13.5	13.5	0.0	8.0	9.0	+1.0	14.6	20.0	+5.4	32.4	34.6	+2.2
9	20	Cor pulmonale	1.8 mg. digitoxin	9.5	8.5	−1.0	4.0	4.0	0.0	15.3	14.0	−1.3	32.1	33.3	+1.2
10	73	Coronary sclerosis	2.4 mg. digitoxin	10.0	10.0	0.0	5.0	5.0	0.0	13.9	12.2	−1.7	27.8	24.2	−3.6
11	46	Thyrotoxicosis	1.6 mg. digitoxin	11.5	11.5	0.0	6.0	5.0	−1.0	12.3	14.5	+2.2	35.8	33.4	−2.4
12	67	Hypertensive cardiovascular disease	2.2 mg. digitoxin	14.0	14.0	0.0	5.0	6.0	+1.0	13.5	13.9	+0.4	27.7	30.8	+3.1
13	52	Myocardial infarction	2.4 mg. digitoxin	11.0	14.0	+3.0	8.0	7.0	−1.0	16.4	13.6	−2.8	36.9	34.9	−2.0
14	43	Hypertensive cardiovascular disease	1.6 mg. lanatoside C 1.2 mg. digitoxin	16.0	13.0	−3.0	9.0	8.0	−1.0	14.0	12.7	−1.3	26.1	24.3	−1.8
15	49	Myocardial infarction	2.4 mg. digitoxin	20.5	19.5	−1.0	10.0	11.0	+1.0	14.5	13.8	−0.7	27.5	26.1	−1.4
16	51	Rheumatic heart disease	2.4 mg. digitoxin	10.5	9.5	−1.0	5.0	5.0	0.0	20.5	13.5	−7.0	35.0	35.1	+0.1
17	66	Myocardial infarction	1.7 mg. digitoxin	16.0	8.5	−7.5	6.0	6.0	0.0	12.6	14.4	+1.8	23.2	22.7	−0.5

TABLE 2.—*Normal Subjects before and after Digitalization*

Subject No.	Age (years)	Total Digitalis	Clotting Time of Blood (Minutes)						Prothrombin Time of Plasma (Seconds)					
			Lee-White Method			Leifer Method			Undiluted Plasma			12.5% Plasma		
			Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change
1	25	20 U. digitalis	16.25	15.0	−1.25	9.5	9.0	−0.5	12.0	12.9	+0.9	28.1	31.8	+3.7
2	25	18 U. digitalis	18.5	14.5	−4.0	9.0	10.0	+1.0	13.1	13.2	+0.1	32.1	34.2	+2.1
3	25	20 U. digitalis	14.5	16.5	+2.0	10.0	9.0	−1.0	13.0	14.9	+1.9	25.9	31.7	+5.8
4	24	21 U. digitalis	17.5	15.0	−2.5	9.0	9.0	0.0	12.8	13.1	+0.3	27.6	32.7	+5.1
5	24	2.0 mg. digitoxin	12.75	8.5	−4.25	6.5	5.0	−1.5	12.2	13.6	+1.4	29.8	31.0	+0.2
6	22	2.0 mg. digitoxin	8.5	9.0	+0.5	5.0	5.0	0.0	15.0	14.9	−0.1	42.5	36.3	−6.2
7	22	2.0 mg. digitoxin	9.0	8.0	−1.0	4.0	4.0	0.0	11.9	12.9	+1	31.3	28.6	−2.7
8	22	2.0 mg. digitoxin	8.5	8.5	0.0	5.0	4.0	−1.0	12.9	17.1	+4.2	37.1	39.9	+2.8
9	21	2.0 mg. digitoxin	9.0	9.0	0.0	5.0	5.0	0.0	13.2	15.1	+1.9	30.7	27.9	−2.8
10	22	1.8 mg. digitoxin	10.0	9.0	−1.0	5.0	5.0	0.0	13.4	15.0	+1.6	37.5	34.4	−3.1
11	22	2.0 mg. digitoxin	9.0	9.0	0.0	6.0	6.0	0.0	13.3	13.6	+0.3	34.5	32.9	−1.6
12	22	2.2 mg. digitoxin	8.75	9.0	+0.25	5.0	5.0	0.0	12.3	12.2	−0.1	32.9	33.1	+0.2
13	24	1.8 mg. digitoxin	19.0	18.0	−1.0	9.5	9.0	−0.5	14.6	14.1	−0.5	30.7	33.0	+2.3
14	24	2.0 mg. digitoxin	16.5	17.0	+0.5	7.0	9.0	+2.0	13.1	13.0	−0.1	28.8	30.0	+1.2
15	24	2.0 mg. digitoxin	14.5	17.5	+3.0	7.0	7.0	0.0	13.0	13.0	0	31.8	33.2	+1.4
16	24	1.8 mg. digitoxin	17.75	14.5	−3.25	8.5	10.0	+1.5	13.2	10.4	−2.8	31.5	28.1	−3.4
17	24	2.0 mg. digitoxin	17.5	14.5	−3.0	8.0	6.0	−2.0	11.9	11.9	0	32.9	33.2	+0.3
18	24	1.8 mg. digitoxin	10.0	10.0	0.0	5.0	5.0	0.0	14.2	12.3	−1.9	31.8	34.7	+2.9
19	24	1.8 mg. digitoxin	9.0	10.0	+1.0	5.0	5.0	0.0	13.8	13.2	−0.6	37.3	34.3	−3.0
20	24	1.8 mg. digitoxin	10.0	9.0	−1.0	5.0	6.0	+1.0	13.5	13.1	−0.4	33.6	31.7	−1.9
21	32	3.0 mg. digitoxin	9.0	16.0	+7.0	5.0	7.0	+2.0	12.5	13.7	+1.2	33.2	32.4	−0.8

TABLE 3.—*Normal Controls—Undigitalized*

Control No.	Age (years)	Diagnosis	Clotting Time of Blood (Minutes)						Prothrombin Time of Plasma (Seconds)					
			Lee-White Method			Leifer Method			Undiluted Plasma			12.5% Plasma		
			Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change
1	27	Normal	11.5	9.0	−2.5	5.0	5.0	0	12.4	12.6	+0.2	27.3	30.3	+3.0
2	70	Marginal gastric ulcer	11.0	9.5	−1.5	5.0	5.0	0	13.2	14.5	+1.13	27.2	26.4	−0.8
3	35	Epilepsy; anxiety state	13.5	11.5	−2.0	5.0	8.0	+3.0	13.9	12.2	−1.7	29.8	25.8	−4.0
4	21	Pericarditis	12.0	14.5	+2.5	6.0	8.0	+2.0	14.5	13.4	−1.1	30.4	28.7	−1.7
5	47	Gastric ulcer	8.5	10.0	+1.5	6.0	5.0	−1.0	12.4	13.6	+1.2	30.0	29.0	−1.0
6	45	Malaria	9.0	14.0	+5.0	7.0	7.0	0	13.0	14.4	+1.4	27.0	26.5	−0.5
7	53	Myocardial infarction	9.5	10.0	+0.5	5.5	5.0	−0.5	17.8	13.7	−4.1	28.0	32.8	+4.8
8	49	Lobar pneumonia	11.5	9.5	−2.0	6.0	5.0	−1.0	13.5	13.7	+0.2	27.3	27.8	+0.5
9	65	Coronary sclerosis	11.5	12.0	+0.5	7.0	8.0	+1.0	15.0	13.7	−1.3	25.5	32.8	+7.3
10	42	Duodenal ulcer	9.5	9.5	0.0	5.0	5.0	0	11.9	12.3	+0.4	28.8	32.6	+3.8
11	78	Coronary heart disease	11.0	13.0	+2.0	5.0	7.0	+2.0	13.3	15.0	+1.7	26.4	34.2	+7.8
12	13	Acute glomerulonephritis	11.5	11.5	0	5.0	8.0	+3.0	13.4	12.9	−0.5	35.5	39.6	+4.1
13	32	Normal	9.5	9.0	−0.5	6.0	5.0	−1.0	13.3	12.5	−0.8	33.0	33.2	+0.2

a change of −0.8 seconds or −5 per cent. In the same group of patients with 12.5 per cent plasma the average times before and after digitalization were 32.3 seconds and 30.0 seconds respectively, a change of −2.3 seconds or −7 per cent.

In the group of normal subjects who were digitalized the average initial time with 100 per cent plasma was 13.1 seconds, the average final time 13.5 seconds, a change of +0.4 seconds or +3 per cent.

In the control group the average initial time with undiluted plasma was 13.6 seconds, the final time 13.4 seconds, a change of −0.2 seconds or −2 per cent. With 12.5 per cent plasma the average times were 28.9 seconds and 30.7 seconds, an average change of +1.8 seconds or +6 per cent.

As in the case of the coagulation times, there appeared to be no constant trend toward either a prolongation or a shortening of the prothrombin time. The average time at the start of the study was comparable in all groups and the daily average changes following digitalization were small and of no greater degree than those noted in patients who received no digitalis. Essentially the same results were noted using both diluted and undiluted plasma.

None of the differences observed, either in clotting or prothrombin times, were statistically significant.

Conclusions

The action of digitalis on the clotting time and prothrombin time was investigated in 17 cardiac patients in congestive heart failure and in 21 normal subjects to determine the effect of this drug, in therapeutic doses, on the clotting function of the blood.

There were no statistically significant changes in either clotting or prothrombin times following the administration of digitalis.

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