

VARIATION OF THE FIBRINOGEN CONCENTRATION IN THE BLOOD AFTER INTRAVENOUS INJECTION OF THROMBIN IN ANIMALS THAT RECEIVED DICOUMARIN

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Direct-action anticoagulants (dicoumarin, phenyllin, and their derivatives) have been in clinical use for several years for the prevention of thrombus formation. However, in a number of cases thrombosis develops in spite of the use of these anticoagulants [1, 4, 7].

The purpose of this work is to compare the action of thrombin on control animals and on animals that had received dicoumarin or phenyllin. The experiments were conducted with dicoumarin and phenyllin, since they are the Soviet-produced direct-action anticoagulants most widely used in the clinic.

EXPERIMENTAL METHOD

The experiments were conducted on white male rats weighing 180-200 g. The first group of experimental animals received peroral administration of 5 mg of dicoumarin or 10 mg of phenyllin in the form of a suspension on the eve of the experiment. The animals of the second group received the anticoagulant over a period of three days (5 mg on the first day and 2 mg each on the second and third days). The control rats received the corresponding amount of physiological saline. The dose of thrombin, injected into the jugular vein, was selected so that the total time of clotting in the control rats would be lengthened to 3-6 min.

TABLE 1. Change in the Fibrinogen Concentration as a Result of Intravenous Injection of Thrombin

Conditions of experiments	No. of animals	Prothrombin time (in % of time before injection of thrombin)	Prothrombin time with activated thrombo-plastin (in % of time before injection of thrombin)	Fibrinogen concentration before injection of thrombin (in mg %)	Fibrinogen concentration 6 min after injection of thrombin (in mg %)	Decrease in fibrinogen 6 min after injection of thrombin (in %)
Control	77	100	100	355	237	33
Animals that received dicoumarin on the eve of the experiment . . .	97	25-12.5	25-12.5	335	34	90
Animals that received dicoumarin over a period of three days.	30	Below 12	Below 12.5	380	266	30

TABLE 2. Change in the Total Clotting Time, Prothrombin, Thrombin Time, and Generation of Thromboplastin after Injection of Thrombin

Conditions of experiments	No. of animals	Time of blood collection	Total clotting time	Prothrombin time	Thrombin time	Minimum clotting time in tests of generation of thromboplastin
				in sec		
Control	25	Before injection of thrombin	120	15-16	26	9
		6 min after injection of thrombin	120-360	20-26	30-40	14-24
Animals that received dicoumarin on the eve of the experiment	30	Before injection of thrombin	120-180	20-45	26	9
		6 min after injection of thrombin	> 1800	> 180	> 180	> 50
Animals that received dicoumarin for 3 days before experiment.	25	Before injection of thrombin	240-480	35-70	26	9
		6 min after injection of thrombin	240-480	60-70	30-40	14-24

Blood was taken from the jugular veins of the animals before and 6 min after the injection of thrombin (in portions of 0.2 ml for determination of the total clotting time and 1 ml with sodium oxalate). The fibrinogen concentration was determined according to Bidwell [5], test of thromboplastin generation according to Biggs and Douglas [6], total clotting time according to Lee and White [2], and prothrombin time according to the one-step time of Quick [3]. As is well known, the latter method permits a detection of the concentration in the blood of prothrombin, thrombotropin and factors VII, IX, and X, which are changed by the introduction of dicoumarin. The following modification of this method, which can be used to obtain an idea of the change in prothrombin itself, has been developed for a more complete characterization of the action of dicoumarin. A mixture of different volumes of thromboplastin, calcium chloride, and normal rat blood serum, diluted 5-fold, was incubated for 2 min at 37°. One volume of the test plasma was added to the mixture, and its clotting time was determined. In this modification, the degree of increase in the duration of clotting does not depend upon the decrease in the concentration of thromboplastin activating factors (since they were introduced with the serum in excess), but reflects the change in prothrombin itself.

For this time we constructed a dilution curve, analogous to the usual dilution curve of the prothrombin time, and expressed the results in percent.

EXPERIMENTAL RESULTS

From the data presented in Table 1, it follows that after the administration of thrombin, the fibrinogen concentration dropped considerably more in the rats that had received a single dose of dicoumarin than in the control animals or in the rats that had received dicoumarin for three days.

From Table 2 it is evident that after the injection of thrombin, all the indices in the experimental rats that had received dicoumarin on the eve of the experiment were changed more substantially than in the controls and in animals that had received dicoumarin for three days.

The experimental results show that during the first day after injection of a single dose of dicoumarin (or phenyllin), intravenous injection of thrombin gives rise to a more substantial drop in the fibrinogen level than in the control animals. Animals that received anticoagulant for three days reacted to intravenous injection of thrombin just like the controls. In the control rats, the total clotting time 3 min after the injection of thrombin, as corresponds to the literature data, was the same as after 6 min. In the experimental rats of the first group, in approximately 50% of the cases, after 3 min the total clotting time was 15-20 sec, i.e., in all probability active thrombin

was present in the blood. In the experimental rats of the second group, the total clotting time was shortened by 2-3 min in comparison with the time before the injection of thrombin.

SUMMARY

Albino rats ranging in weight from 180 to 200 g were given dicoumarin per os. The first group of animals were given a single 5 mg dose of the preparation shortly before the experiment. To rats of the second group dicoumarin was administered during three days: a 5 mg dose on the first day, and a 2 mg dose on the second and third day before the experiment. On the day of the experiment the rats were given thrombin intravenously; the fibrinogen content of the blood was examined before and six minutes after the injection, as well as changes in the following tests were studied: total time of coagulation, prothrombin time, thrombin time, and the time of thromboplastin generation. It was found that within the first 24 h of administration of a single dicoumarin dose the intravenous injection of thrombin caused in the test animals a larger decline of fibrinogen concentration than in the control animals. The animals given dicoumarin during three days reacted to intravenous thrombin injection in the same way as the control rats.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
