Comparative Effects of Dicoumarol, Tromexan, and Heparin on Thrombus Propagation *

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RECENTLY we have reported a method of producing a relatively standard degree of venous thrombosis.[6] Heparin was subsequently found to be superior to dicoumarol, coumadin, and tromexan in preventing these experimentally induced thrombi.[7] Further studies have shown that these thrombi, once produced, will propagate to several times their original size in a period of 48 hours. The present report is of the effect of heparin, dicoumarol, and tromexan on the prevention of clot propagation.

Methods

As in previously reported experiments [6] the external jugular veins of mongrel dogs weighing from 16 to 20 kilograms were used. Several centimeters of the vein were dissected completely from surrounding tissue and a small lucite cuff passed around the vein. Two platinum electrodes were included within these cuffs. A current of 5 milliamperes was passed between them for one hour in all experiments. Venous stasis and vein wall pulsations were carefully controlled as in previous experiments. The experimental thrombi produced by this method have an average size of 4×12 mm. at the end of one hour of current application.[6]

To determine whether thrombus propagation would occur, the wounds in 12 dogs were closed very carefully with silk after a thrombus was produced. The neck wounds were reopened in 48 hours. Of the first four animals, two showed propagation of the thrombus to 40 and 50 mm. in length. The other two had no thrombus present. A small embolus was found in the right lung of one. It was observed that, in the two animals in which the thrombus had remained intact, a small branch of the external jugular vein had been included accidentally at the site of the electrodes. In the subsequent eight control experiments, a small side branch was included purposely at the electrode site. These eight showed clot propagation in 48 hours with a range of 25 to 70 mm. and an average length of 40.5 mm. (Fig. 1). The inclusion of a small side branch appeared to act as an anchor which holds the original thrombus during the subsequent propagation.

To determine the effect of heparin, dicoumarol, and tromexan on thrombus propagation a "primary" thrombus was induced in each of 20 dogs. In eight, aqueous heparin was given immediately after closure of the neck wound. Repeated small doses of heparin sufficient to maintain the coagulation time between two and four times the pre-heparin value were given during the following 48 hours. In the other 12 dogs the prothrombin value was decreased below 30 per cent of normal with dicoumarol or tromexan before the initial thrombus was induced. The prothrombin time was maintained between 12 and 30 seconds (prothrombin value between 30 and 3% of normal) for the following 48 hours.

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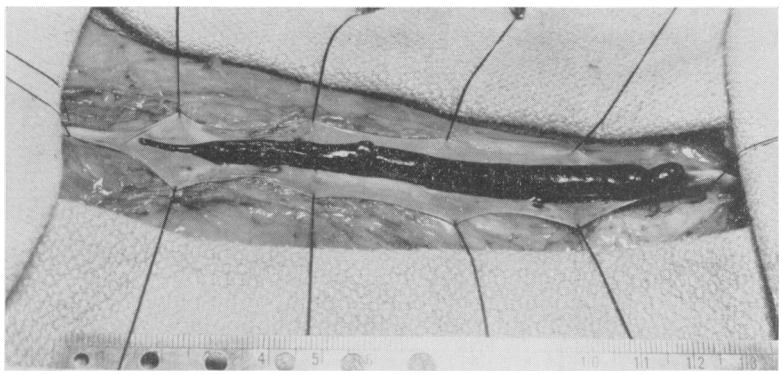

FIG. 1. An opened external jugular vein 48 hours after induction of thrombosis. Note that the original thrombus, the one-centimeter wrinkled area at the inferior (left) end, has progagated to several times its original size.

Coagulation times were determined by a modification of the method of Lee and White [2] and prothrombin determinations were made by the one-stage method of Quick,[4] using Simplastin.® The coagulation time was determined every four hours in the heparin experiments. The coagulation time was prolonged between two and four times the preheparin value with 0.75 mg./kg. of aqueous heparin * given every four hours. Eight dogs were given small doses of dicoumarol (12 to 50 mg. daily) for four to 12 days. After the prothrombin had been stabilized below 30 per cent of normal for 48 hours the primary thrombus was electrically induced. The prothrombin value remained below 30 per cent of normal during the ensuing 48 hours. Four dogs were given a single dose (50 to 125 mg.) of tromexan. Twenty-four hours later when the prothrombin times were between 14 and 16 seconds (between 20 and 18% of normal) the primary thrombus was induced. The prothrombin value remained below 30 per cent of normal for the subsequent 48 hours.

* The heparin used in the experiments was kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

Results

In the eight animals treated with heparin, the original thrombus enlarged in only one (Table 1). The clotting time in this animal was difficult to control and was not maintained in a therapeutic range during most of the 48-hour period. In four of the animals there was no clot present. It had either been lysed or had broken loose into the circulation. No thrombi were found in the lungs. In three others the clot had not enlarged and averaged only 12 mm. in greatest dimension.

In the eight animals given dicoumarol and in which the prothrombin value was below 30 per cent of normal both before and after the production of the primary thrombus, the electrically induced thrombi were 25 to 44 mm. with an average clot

TABLE 1

	No. Experiments	No. Propagated Thrombi	Average Length of Thrombus (mm.)
Control	12	10*	40.5
Heparin	8	1	—
Dicoumarol	8	7	37
Tromexan	4	2	44

* 2 controls not propagated—initial thrombus detached.

length of 37 mm. In the experiment in which clot propagation failed to occur, the prothrombin time was maintained between 20.5 and 25 seconds (prothrombin value between 10 and 6% of normal).

In the four animals given tromexan the thrombi propagated on only two. These thrombi measured 55 and 33 mm. in length. In all four animals, the prothrombin times were always greater than 14 seconds (prothrombin value less than 20%) during the entire experiments. Thrombosis was induced when the prothrombin time was increasing and had reached 14 and 16 seconds (20 to 18%). Over the next 48 hours a further increase to 27 and 29 seconds (both less than 5% prothrombin value) occurred. The Lee and White clotting time was also elevated to one and one-half times the pre-tromexan value in the two dogs in which propagation failed to occur.

Discussion

The relative value of heparin and coumarin derivatives in the treatment of venous thrombosis is still a subject of debate. The major problem in evaluating different anticoagulants has been a lack of either comparable clinical controls or a satisfactory method of producing thrombosis in animals. In the reported experimental evaluation of the commonly used anticoagulants, their effect on propagation has not been determined adequately.[1, 2, 5] Anticoagulants are usually used clinically to prevent propagation of a thrombus that has already developed.

The experiments reported here strongly suggest two important factors in anticoagulant therapy which is directed toward the prevention of thrombus propagation. First, heparin prevents propagation of a thrombus if the Lee and White clotting time is kept elevated to at least one and one-half times the pre-heparin level. Failure to maintain an elevated clotting time allows thrombus propagation. Secondly, both tromexan and dicoumarol fail to prevent thrombus propagation, unless the prothrombin value is dangerously depressed. Values between 20 and 30 per cent of normal prothrombin were associated consistently with progressive thrombosis in these experiments. With dicoumarol, even with prolonged therapy prior to induction of the initial thrombus, propagation occurred unless the prothrombin value was maintained below 10 per cent of normal (prothrombin time over 20 seconds). Four of the eight dogs were maintained below 20 per cent normal prothrombin for 48 hours but thrombus propagation still occurred. A marked hemorrhagic tendency was noted usually when the prothrombin value was maintained below 20 per cent of normal.

Many of the initial experiments with thrombus propagation using tromexan or dicoumarol had to be discarded. Either a massive hematoma developed in the neck wound when the prothrombin was below 20 per cent or the prothrombin value would not be kept below 30 per cent during the 48 hours after production of the original thrombus. The maintenance of a prothrombin value between 20 and 10 per cent of normal was difficult in these experiments. Clinical experience in patients has shown also that the maintenance of prothrombin values consistently below 20 per cent is both difficult and dangerous. As a result, prothrombin values are often permitted to range from 20 per cent to 40 or 50 per cent. The value of a prothrombin depression of this degree in preventing thrombus propagation is doubtful. These experiments suggest the need for a further re-appraisal of heparin and coumarin derivatives as therapeutic agents in venous thrombosis.

Summary and Conclusions

A standard venous thrombosis can be produced in the external jugular vein of the dog. This thrombus invariably prop-

agates within 48 hours to several times its original size if it is not detached from the vein wall. Thrombus propagation is prevented by heparin if the Lee and White clotting time is kept elevated above one and one-half times the pre-heparin value. Propagation is not prevented by dicoumarol or tromexan unless prothrombin values well below 20 per cent are maintained. These studies suggest the need for further experimental study and a clinical reappraisal of the relative values of heparin and coumarin like anticoagulants.

References

1. Dale, D. Ursula and L. B. Jaques: The Prevention of Experimental Thrombosis by Dicoumarin. Canad. M. Assn. J., **46**:546, 1942.
2. Lee, R. I. and P. D. White: A Clinical Study of the Coagulation Time of Blood. Am. J. Med. Scien., **145**:495, 1913.
3. Moses, C.: Effect of Heparin and Dicoumarol on Thrombosis Induced in the Presence of Venous Stasis. Proc. Soc. Exper. Biol. & Med., **59**:25, 1945.
4. Quick, A. J.: The Physiology and Pathology of Hemastasis, Philadelphia, Lea and Febiger, pp. 129–130, 1951.
5. Sewell, P., T. Pilkington, and B. Robinson: Heparin and Ethylbiscoumacetate in Prevention of Experimental Venous Thrombosis. Brit. M. J., **1**:1013, 1954.
6. Williams, R. D. and L. C. Carey: Studies in the Production of "Standard" Venous Thrombosis. Ann. of Surg., **149**:3, 1959.
7. Williams, R. D. and D. W. Elliott: The effects of Heparin and Coumarin Derivatives on a Standarized Intravenous Thrombosis. Surg. Forum IX, pp. 138–142, 1959.