Effect of Anticoagulants on Recanalisation

BY ALEXANDER TAYLOR, M.B., CH.B., AND HIRAM E. ESSEX, PH.D.

Reports have appeared stating that the time required for recanalisation of a vessel occluded by an experimental thrombus is decreased when an anticoagulant of the coumarin variety is administered. The experiments described here were undertaken to verify such reports.

THE use of anticoagulant drugs in the therapy or prevention of thromboembolic conditions has been advocated because such drugs are known to prevent or lessen intravascular thrombosis and extension of a thrombosis. Wright, Kubik and Hayden have shown, moreover, that ethyl biscoumacetate (Tromexan) promotes recanalisation of a vein or artery occluded by a thrombus. In order to test their findings additional studies were carried out.

METHODS

Albino rabbits weighing from 2.5 to 4.0 Kg. and eating a standard diet were used. An ear of each rabbit was shaved and a portion of a peripheral or marginal vein 2.5 cm. in length was isolated by means of black silk or cotton ligatures, perforating the ear and surrounding the vein. The ligatures were prevented from cutting into the veins by placing under them on both surfaces of the ear parallel to the vein, short pieces of small caliber polyethylene tubing. A minute quantity of a thrombin solution (1,000 units of thrombin/ml. saline) was then injected through a no. 25 hypodermic needle into the isolated vein segment. Thrombosis occurred almost immediately. In an attempt to prevent the escape of thrombin into the general circulation through anastomotic channels, a large sheathed, curved clamp was applied to each ear immediately before the injection of thrombin, in such a way as to completely isolate the venous segment. It was kept in place for approximately 10 min. Twenty-four hours later the ligatures were removed and in approximately 65 per cent of instances, an intravenous clot of desired length adherent to the vessel wall remained. In the other 35 per cent of the rabbits used, the thrombus was either too short, too extensive, or became detached after removal of the ligatures.

The intravenous thrombi were proved to occlude the veins completely by roentgenographic demonstration that radiopaque fluid introduced into the peripheral ear vein of the anesthetized animals distal to the thrombus failed to pass through the vein in the region of the obstruction, but rather proceeded proximally through collateral veins. Small metal V-shaped arterial clips were used to indicate on the phlebogram what was considered to be the length and site of the thrombus. To demonstrate the length of the clot, the ear was also transilluminated and photographed. The site and length of the clot were indicated by the increased opacity in this region.

RESULTS AND DISCUSSION

A method for inducing thrombi of desired length having been achieved, an attempt was then made to ascertain the average time required for its recanalisation. A radiopaque medium (Diodrast) was gently introduced into the thromboed veins distal to the thrombus at intervals of 1 or 2 days and phleograms made. In each instance serial phleograms revealed gradual lysis of the clot with final complete recanalisation permitting the contrast medium to flow through it rather than through collateral channels. There was a remote possibility that a vein in the region of the clotted one had assumed the function of the clotted vein. The time required for recanalisation in 13 control animals varied from 11 to 19 days; the average was 14.6 days.

The venous channel was demonstrated before thrombosis was induced, occlusion of the venous channel was demonstrated, and recanalisation was demonstrated (fig. 1).

The next project was to determine the effect, if any, of bishydroxycoumarin (Dicouma-
rol) and ethyl biscoumacetate (Tromexan) on the rate of recanalisation. Tablets of these anticoagulants were crushed and enough distilled water was added to the powder to make a suspension. This was then introduced into stomachs of the experimental animals using a stomach tube and syringe: Dieumarol 100 mg./Kg. daily, Tromexan 300 mg./Kg. daily. Doses of this magnitude were used initially as such doses of Tromexan had been used in the original study of Wright, Kubik and Hayden. Daily prothrombin times were not determined. The administration of Dieumarol and Tromexan was begun within 24 hours of the removal of the ligatures and immediately after the first phlebogram, demonstrating the thrombotic obstruction, had been prepared. Phlebograms were made thereafter at intervals of 2 days or less. Studies on 10 rabbits indicated that the time required for recanalisation of veins obstructed by an experimental thrombus varied from 4 to 8 days with an average time of 6.2 days. The number of animals dying of hemorrhage was so great it was decided to prepare a new series of 10 rabbits and to attempt to control the dosage of anticoagulants by regular prothrombin determinations. The initial dose was identical to that described above, but maintenance doses of Dieumarol varied from 25 to 100 mg./Kg. daily, and of Tromexan from 50 to 300 mg./Kg. daily. On some days, depending on the prothrombin time, no anticoagulant was administered. The percentage of normal prothrombin activity and the time required for recanalisation are presented in table 1.

It was found that the response of the prothrombin time of the plasma of these rabbits to Dieumarol and Tromexan varied considerably and difficulty was experienced in attempting to keep the prothrombin time within the "therapeutic range." Within the range obtained, however, it was demonstrated once again that the rate of recanalisation was considerably faster in animals receiving Dieumarol or Tromexan, the average time being 5.5 days, as contrasted with the average time of
TABLE 1.—Time Required for Recanalisation of Experimentally Thrombosed Veins of Animals Receiving Anticoagulant Drugs

<table>
<thead>
<tr>
<th>Drug administered</th>
<th>Percentage of normal prothrombin activity</th>
<th>Days of anticoagulant administration</th>
<th>Days required for recanalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tromexan</td>
<td>100</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Tromexan</td>
<td>100</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Tromexan</td>
<td>10</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Dicumarol</td>
<td>100</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

Average number of days required for recanalisation, 5.5

14.6 days required in animals which did not receive Tromexan or Dicumarol.

SUMMARY

Recanalisation of an experimentally thrombosed vein in the rabbit occurs much more rapidly when the animal is receiving anticoagulant drugs of the coumarin variety. These data confirm the results of a somewhat similar study previously conducted by Wright and associates.

SUMMARY IN INTERLINGUA

Le recanalisation de un experimentalmente thrombotic vena de conolio occurre multo plus rapidemente quando le animal recipe drogas anticoagulante del typo coumarinie. Iste constatation confirma le resultatos de un plus o minus simile studio conduite previemente per Wright e su associatos.

REFERENCES

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