Effect of Anticoagulants on Experimental Cerebral Infarction

Clinical Implications

By Jack P. Whisnant, M.D., M.S., Clark H. Millikan, M.D., George P. Sayre, M.D., M.S., and Khalil G. Wakim, M.D., Ph.D.

Cerebral infarction is attended by extravasation of blood in varying degrees. The present study was undertaken to learn whether anticoagulant therapy increases the extravasation and thereby diminishes or negates possibly favorable therapeutic effects. A series of experiments on dogs is described and the clinical implications are discussed.

The use of anticoagulant therapy in cerebrovascular disease has become a widely, though not universally, accepted practice. There are specific categories of cerebrovascular disease in which anticoagulant therapy has seemed definitely beneficial. Clinical interest in this field led us to carry out a series of experiments to obtain evidence in regard to the effect of anticoagulant therapy on completed cerebral infarction in dogs. Blumgart and associates have studied the effects of bishydroxycoumarin (Dicumarol) immediately after myocardial infarction in dogs. A comparison of the results with those in a control group did not show a difference in the hemorrhagic extravasations in the infarcts nor in the size of the infarcts. The difference in the structure of the brain as compared to the heart warrants further investigation in regard to the effects of anticoagulants on cerebral infarction. This report is a compendium in which we have brought together our accumulated experience on this subject. We shall indicate that there is, indeed, an increased risk in administering anticoagulants under the conditions of these experiments, and shall emphasize its clinical implications.

Methods

Two methods have been used for the production of experimental cerebral infarction in dogs. With either method infarction has developed in 70 to 80 per cent of the animals. The first method was the introduction, into one internal carotid artery in the neck, of approximately 0.2 ml of liquid vinyl acetate* through a 20-gage needle. This material polymerized or hardened when it came in contact with the blood and formed a more or less continuous strand of solid material in the internal carotid and middle cerebral arteries and sometimes extended into the anterior cerebral and posterior communicating arteries. Therefore, it did not represent an embolus in the usual sense, but it did occlude a relatively long segment of the vascular tree to the brain on one side. It was rarely found in the opposite side of the circle of Willis.

The second method was the introduction, through a 20-gage needle, of 0.2 ml of 48-hour-old autologous clot into 1 internal carotid artery in the neck. Venous blood was obtained 2 days prior to the operative procedure and allowed to clot at room temperature in a sterile tube. We found that 48 hours was the optimal time to use the clotted blood for this purpose. The clot was blotted dry and small fragments of it were placed in a 1-ml syringe to a total amount of 0.2 ml. When the material was introduced into the internal carotid artery through a 20-gage needle, the clot fragments stopped in various places, especially at bifurcations of the cerebral arteries. This, therefore, represented the injection of multiple clot emboli into one internal carotid artery. Rarely did these embolic fragments go into arteries on the opposite side of the circle of Willis.

Results

Examination of the brains at necropsy revealed the infarcts, with or without anticoagulants, to be partly pale and partly hemorrhagic. In order to record the extent of an

*Vinyl acetate for this study was obtained from Ward's Natural Science Establishment, Rochester, N. Y.
infarct and the extent of hemorrhagic infarction for comparison, we cut each brain into 7 standard coronal slices. A scale drawing was made representing each coronal slice and these were reproduced on printed forms so that each infarct could be depicted in its total extent and its extent of hemorrhagic infarction. These areas were then traced with a planimeter to measure the total areas involved on the 7 coronal slices, and from these figures the percentage of hemorrhage in an infarct was computed. The limitations of such a scheme are obvious, but it has proved useful to compare various infarcts by numerical figures rather than by visual impressions.

Practically all of the infarcts produced by vinyl acetate were less than 30 per cent hemorrhagic (table 1). One extremely hemorrhagic lesion in this group was an exception to the relatively pale infarcts produced by this method. Our earlier experience with 37 infarcts produced by injection of vinyl acetate gave further evidence that infarcts produced by this method are relatively nonhemorrhagic.

On the other hand, the infarcts that were produced by injection of autologous blood-clot fragments varied in their hemorrhagic extent, but it was found that two thirds of those that were less than 12 days old were more than 60 per cent hemorrhagic. This would seem to support the contention that embolic infarcts are usually rather hemorrhagic. There were notable exceptions to this finding; in the group studied 2 infarcts were rather pale and 4 had only a mild to moderate hemorrhagic character (table 1).

<table>
<thead>
<tr>
<th>Hemorrhagic area in infarct, (%)</th>
<th>Vinyl acetate</th>
<th>Autologous clots</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of infarcts</td>
<td>Per cent</td>
</tr>
<tr>
<td>0 to 30</td>
<td>13</td>
<td>93</td>
</tr>
<tr>
<td>31 to 60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>61 to 90</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>91 to 100</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

maintenance, depending on the prothrombin time. The prothrombin times were determined by the Quick method as modified by Hurn, Barker, and Magath with use of Difco thromboplastin. The control prothrombin times ranged from 6 to 8 seconds in all animals. In the studies mentioned herein the prothrombin activity is noted in percentage of normal, which was established from a curve made by determining the prothrombin time of serial dilutions of plasma with saline. For example, a prothrombin activity of 20 per cent is equivalent to the prothrombin time obtained with a 20 per cent concentration of normal dog plasma.

Our initial experience in administering anticoagulants to dogs with cerebral infarcts involved 13 animals that were given Tromexan and Dicumarol on the same day the infarcts were produced. The infarcts were produced by intracarotid injection of vinyl acetate, which, as noted previously, caused relatively pale or nonhemorrhagic infarcts. In this group, the prothrombin activity was intentionally maintained excessively low by giving an excessive amount of anticoagulant. The average of the lowest values for each animal was 5 per cent prothrombin activity. Eleven of these infarcts were strikingly hemorrhagic when compared with the relatively pale infarcts in the 13 control dogs. Animals survived at least 30 hours to be included in either group. A considerable range of degree of hemorrhage was noted, often in the same infarct (fig. 1, top). In 5 animals the entire infarct was occupied by hemorrhage, and in 1
TABLE 2.—Effect of Anticoagulants on Extent of Hemorrhage in Cerebral Infarcts Produced by Vinyl Acetate

<table>
<thead>
<tr>
<th>Hemorrhagic area in infarct, (%)</th>
<th>Group of dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Number</td>
<td>Per cent</td>
</tr>
<tr>
<td>0 to 30</td>
<td>13</td>
</tr>
<tr>
<td>31 to 60</td>
<td>0</td>
</tr>
<tr>
<td>61 to 90</td>
<td>0</td>
</tr>
<tr>
<td>91 to 100</td>
<td>1</td>
</tr>
</tbody>
</table>

of these intraventricular hemorrhage was noted.

It was rather obvious that the infarcts were considerably more hemorrhagic in the animals with excessively reduced prothrombin activity than in the controls. We then conducted a similar study, making sure that the prothrombin activities were maintained within a reasonable therapeutic range (10 to 30 per cent). For 2 reasons this study was limited to animals that survived at least 48 hours: (1) so that full anticoagulant activity could be effected, and (2) because most control animals as a result of the infarct died within 48 hours. Therefore the period of high mortality from the infarcts alone was eliminated from this part of the study.

The hemorrhagic zones in these infarcts were mapped on the printed representations of the standard brain slices and were compared to similar regions in a group of 14 control animals (table 2). It was apparent that the infarcts in the group that received anticoagulants were significantly more hemorrhagic than those in the control group. However, 1 cortical infarct in the control group was almost entirely hemorrhagic, though not densely so, and infarcts in 2 dogs that received anticoagulants had no hemorrhagic character (fig. 1, bottom). All control animals in this group that lived for 3 days after an infarct was produced survived until termination of the study at 12 days. To the contrary, in the group that received anticoagulants and survived at least 3 days, 8 of 20 animals (40 per cent) died prior to the termination of the study. The conclusion is that the administration of anticoagulants to these animals in-

Fig. 1. Top. Infarct produced with injection of vinyl acetate. Anticoagulants started same day and continued for 12 days, when dog was killed. Margins of infarct are more densely hemorrhagic than remainder of infarct. Bottom. Infarct produced with injection of vinyl acetate. Animal received anticoagulants full period of study (12 days). Completely pale infarct.
creased the hemorrhagic character of their cerebral infarcts and also increased the hazard of death for the animals.

As for the infarcts produced by emboli consisting of autologous blood-clot fragments, it should be kept in mind that these infarcts were ordinarily rather hemorrhagic even without influence from other agents. Twenty dogs received Tromexan and Dicumarol for 48 hours prior to the intracarotid injection of the clot fragments, so that a therapeutic range of reduced prothrombin activity existed at the time the infarct was produced. After the infarcts were produced, the prothrombin activity was maintained close to the therapeutic range (10 to 30 per cent) by oral administration of Dicumarol. The hemorrhagic character of the infarcts was compared with that of the infarcts of 18 control animals in which the infarcts were produced in the same manner, but no anticoagulant was given. The animals receiving anticoagulants were matched with the control group as to the age of the infarcts, which ranged from 8 hours to 12 days.

A wide range in the extent of hemorrhagic character of the infarcts was noted in each group of this study. The percentage of the infarct which was hemorrhagic in the mildly and moderately hemorrhagic infarcts corresponded almost exactly in the control group and the group which received anticoagulants (0 to 90 per cent hemorrhagic). However, 8 of 18 animals in the control series and 12 of 20 in the group which received anticoagulants had infarcts that were more than 90 per cent hemorrhagic (table 3; fig. 2). While these latter figures are suggestive of an adverse effect from the anticoagulants, the differences are not statistically significant in a series of this size. This suggestive adverse effect is perhaps increased by the fact that frank hemorrhage occurred within 2 infarcts in dogs which received anticoagulants, and in 1 of these intraventricular hemorrhage was present. The prothrombin activity in the latter dog was inadvertently reduced to 5 per cent. Frank hemorrhage was not noted in any of the infarcts in the control animals.

The hemorrhagic areas of the experimental animals are tabulated in table 3 with those of the control animals. The differences are statistically significant. 

**Table 3:** Effect of Preinfarction Anticoagulants on Extent of Hemorrhage in Cerebral Infarcts Produced by Clot Fragments

<table>
<thead>
<tr>
<th>Hemorrhagic area in infarct (%)</th>
<th>Control Number</th>
<th>Preinfarction anticoagulants Number</th>
<th>Control Per cent</th>
<th>Preinfarction anticoagulants Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30</td>
<td>2</td>
<td>2</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>31 to 60</td>
<td>4</td>
<td>2</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>61 to 90</td>
<td>4</td>
<td>4</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>91 to 100</td>
<td>8</td>
<td>8</td>
<td>45</td>
<td>60</td>
</tr>
</tbody>
</table>

To get a more comprehensive picture of the effect of anticoagulants on experimental cerebral infarction, we used another group of animals in which we delayed the administration of Tromexan and Dicumarol for 3 days after the infarcts were produced. For this study 48-hour-old autologous clot fragments were injected to produce the infarcts. The therapeutic range of reduced prothrombin activity was achieved within 24 hours; thus the full effect of the anticoagulants first occurred 4 days after the infarcts were produced. A prerequisite for this study was that a dog with an infarct had to survive at least 3 days to be included in either the control group or the group given anticoagulants. Only those dogs with clinically detectable infarcts were used, and thus each animal had hemiparesis or forced circling or both. The incidence of cerebral infarction by these criteria was 70 per cent. A number of dogs died in the first 3 days, usually within 48 hours, and were not used in this part of the study.

Twenty-three dogs were used as controls; 14 were killed when the cerebral infarct was 12 days old and 9 were killed when the infarct was 18 days old. Twenty-eight dogs were started on anticoagulants after 3 days, but 4 of these died before the study ended. One died on the eighth postoperative day as the result of intracerebral hematoma and intraventricular hemorrhage. In 2 animals death resulted from gastrointestinal bleeding on the seventh and ninth postoperative days respectively. Paradoxically, even with the severe gastrointestinal bleeding and rather large
cerebral infarcts, these infarcts were only minimally hemorrhagic, one being 14 per cent and the other 4 per cent hemorrhagic. In all 3 animals which died, the prothrombin activity had dropped to less than 5 per cent sometime during the period of observation. The fourth animal died of meningitis on the fifth postoperative day. Of the other 24 animals given anticoagulants, 15 animals were treated for 9 days, making the infarcts 12 days old, and 9 animals were treated for 15 days, making the infarcts 18 days old, when the animals were killed.

Most infarcts in the control animals were only mildly hemorrhagic. However, 17 per cent of the dogs which received anticoagulants had infarcts that were more than 60 per cent hemorrhagic, while none of the infarcts in the control group was more than 60 per cent hemorrhagic. Stated in another way then, 4 of the dogs given anticoagulants had infarcts which were more hemorrhagic than the most hemorrhagic infarct of the control group (table 4). Besides the 1 dog already noted which died as the result of an intracerebral hematoma, there were 2 other dogs in the group given anticoagulants which had gross hematomas in their cerebral infarcts and survived (fig. 3, top). The prothrombin activity in both of these dogs was less than 5

Fig. 2. a. Control hemorrhagic infarct produced by clot fragments. b. Infarct produced by clot fragments. Animal received anticoagulants starting 2 days before infarct was produced.
per cent. No hematomas were noted in the control animals. In all of our studies of anticoagulants, regardless of how low the prothrombin activity was reduced, we did not see hemorrhage in the brain of an animal except when it was within an infarct or had ruptured from such an infarct into the ventricles.

It may be noted that in this study neither the control animals nor the animals given anticoagulants had infarcts which were as hemorrhagic as even the control animals in the previously cited study with infarcts from clot fragments (table 3). This is apparently because of the age of the infarcts, since in the earlier study (table 3) the ages of the infarcts averaged 1 week, while in this study (table 4) the average age of the infarcts was more than 2 weeks. Apparently this difference in time is adequate for absorption of part of the hemorrhagic element of the infarcts, in spite of continued administration of the anticoagulant.

In order to estimate whether the animals which received anticoagulants derived any protection from them in terms of the total areas of infarction, the areas were determined from the 7 coronal brain slices of these animals for comparison with similar slices from control groups. In the group of dogs which received Tromexan and Dicumarol 48 hours prior to intracarotid injection of clot fragments, the prothrombin activity was in therapeutic range at the time of the injection. In these animals the comparison was limited to those infarcts more than 24 hours old, so that they would be well demarcated. A larger percentage of animals given anticoagulants had small infarcts when compared with the control group. Five of the 18 control animals had infarcts which were larger than the largest infarct in the group given anticoagulants (table 5). The largest infarct in the control group had 2317 mm.² of infarction in the 7 brain slices, while the largest infarct in the group given anticoagulants had 1051 mm.²

Thus it would appear that the anticoagulants offered some protection, and one could surmise that some of the clot fragments which might have caused infarction could have proceeded to smaller branches and caused less damage in the animals which received anticoagulants. However, some cerebral infarc-
tion developed in approximately 70 per cent of the animals which received anticoagulants, and this is in accord with the 80 per cent incidence of infarction in the control group.

When the administration of anticoagulants was delayed for 3 days after the infarcts were produced, the size of infarcts did not differ significantly from that of infarcts in the control group (Table 6). In this instance, of course, the infarcts were completed before anticoagulants were started. Therefore, even though the extent of hemorrhagic element was somewhat greater in the infarcts of this group of dogs which received anticoagulants, the hemorrhagic component did not cause any statistically detectable extension of the damaged region.

The dogs that received anticoagulants prior to infarction were operated on while they had significantly reduced prothrombin activities. The operations were performed on the neck to expose the region of the common carotid bifurcation and the nearby branches. This required a moderate amount of dissection. When the prothrombin time was 15 seconds or less, with a control time of 6 to 7 seconds, slight if any difficulty was experienced in controlling bleeding at the time of operation. In this study a prothrombin time of 15 seconds represents approximately 16 per cent prothrombin activity. When the prothrombin time was longer than 15 seconds there was a problem of varying degree with hemostasis. It was never insurmountable at the time of the procedure, but, for example, it was occasionally necessary to apply firm pressure for 5 to 10 minutes on the hole made in the artery by the 20-gage needle to prevent bleeding after injection of the oclusing material.

Another feature of the preoperative anticoagulant therapy, however, is the occurrence of local hemorrhagic complications after treatment and during the period of observation. Twenty-nine animals were operated on while under effective anticoagulant therapy and 9 of these had some form of hemorrhagic complication at or near the operative site. Four animals had moderate bleeding in the neck at the operative site; 1 animal had a large hematoma in the same region; and 4 animals had large hematomas in the neck with extension into the mediastinum. None of these animals had excessively prolonged prothrombin times during the period of observation. Even when a hematoma was present, the skin wound usually healed satisfactorily. When there was no hematoma, the neck wounds healed promptly.

In our search for occluded cerebral arteries after intracarotid injection of the clot fragments, we made a study chiefly of the major cerebral arteries. In both the animals that received and did not receive anticoagulants some of the occlusions were caused only by the 48-hour-old autologous clot fragments that were injected. Under microscopic examination of tissue stained with hematoxylin and eosin, rather homogeneous material was found that stained pale pink and partly or completely filled the involved artery. Usually little reaction was evident between this material and the vessel wall. The material consisted of poorly stained erythrocytes, strands of fibrin and

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**Table 5.** Effect of Preinfarction Anticoagulants on Size of Cerebral Infarcts Produced by Clot Fragments

<table>
<thead>
<tr>
<th>Size of infarct in seven coronal brain slices (mm.²)</th>
<th>Group of dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (20)</td>
</tr>
<tr>
<td>0 to 300</td>
<td>8</td>
</tr>
<tr>
<td>301 to 600</td>
<td>3</td>
</tr>
<tr>
<td>601 to 1100</td>
<td>4</td>
</tr>
<tr>
<td>1101 to 1600</td>
<td>2</td>
</tr>
<tr>
<td>More than 1600</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 6.** Effect of Anticoagulants Given Three Days after Infarction on Size of Cerebral Infarcts Produced by Clot Fragments

<table>
<thead>
<tr>
<th>Size of infarct in seven coronal brain slices (mm.²)</th>
<th>Group of dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (25)</td>
</tr>
<tr>
<td>0 to 200</td>
<td>9</td>
</tr>
<tr>
<td>201 to 500</td>
<td>8</td>
</tr>
<tr>
<td>501 to 1000</td>
<td>4</td>
</tr>
<tr>
<td>1001 to 1500</td>
<td>1</td>
</tr>
<tr>
<td>More than 1500</td>
<td>1</td>
</tr>
</tbody>
</table>
disintegrating leukocytes. Other occlusions were caused by an organizing thrombus attached to the vessel wall with or without the adjacent palestaining homogeneous material just mentioned.

Occluded cerebral arteries were found in approximately 80 per cent of all animals with infarction which did not receive anticoagulants (97 dogs). When the administration of anticoagulants was delayed for 3 days, the percentage of occluded arteries was approximately the same (83 per cent). When the anticoagulants had been given 2 days before cerebral infarction, occlusions were found in only 45 per cent of the animals. It is interesting, however, that even with the prothrombin activity reduced to 10 to 30 per cent at the time of the clot-fragment injection, there was still a significant percentage of animals in which the major cerebral arteries were occluded.

**DISCUSSION**

There is no doubt that under the conditions of these studies, anticoagulants caused an increase in the amount of hemorrhage noted in cerebral infarcts of dogs, regardless of whether the infarcts were produced with injection of vinyl acetate or with autologous blood-clot fragments. This adverse hemorrhagic effect was less apparent in the infarcts produced with clot-fragment emboli, since these infarcts were relatively hemorrhagic even without the administration of anticoagulants. Sibley and associates also concluded that the administration of Dicumarol increased the hemorrhagic component of canine cerebral infarcts produced by embolic clot fragments.

Since the experimental evidence presented here is unfavorable in regard to anticoagulants given for completed infarction, it is necessary to differentiate this situation from the clinical conditions in which anticoagulants are now used. The current indications for anticoagulant therapy in cerebrovascular disease have recently been pointed out: (1) intermittent insufficiency in the vertebral-basilar circulation, (2) intermittent insufficiency in the carotid system, (3) thrombosis in the vertebral-basilar system with infarction, and (4) actively advancing occlusion of the carotid system. The adverse hemorrhagic infarction we have noted in dogs should not in any respect preclude the use of anticoagulants in the first 3 categories mentioned. The first 2 indications deal entirely with prevention of infarction and the third indication, basilar thrombosis, deals primarily with frequently fatal infarction in the brain stem, which, in our experience, is less likely to be hemorrhagic. Anticoagulant therapy also has decreased the mortality figures so much for basilar thrombosis, that any presumed risk from anticoagulants appears justified. The fourth indication also is primarily prevention, that is, prevention of complete infarction from progressive thrombosis. In such instances the cerebral infarction already present is small or at least incomplete. However, in this category there is reason to draw clear lines in regard to accuracy of diagnosis, before the administration of anticoagulants.

We have accepted as valid a fifth indication for use of anticoagulants, that is, multiple thromboembolic episodes, because of the evidence presented by McDevitt and associates. Our own experience in this category has been only fragmentary. Again, increased hemorrhage in the experimental canine cerebral infarcts should not militate against the use of anticoagulants in this category, since the favorable evidence that has been presented is in regard to prevention of anticipated thromboembolic episodes. Our experiments would point out some potentially unfavorable possibilities, if the anticoagulants were started within 3 days of a previous cerebral infarct.

In our experimental setup, there are differences from the potential clinical situations which should be pointed out. In the first place, with the 48-hour autologous clot, we have injected multiple emboli, frequently resulting in multiple or massive infarcts. This is in contrast to the usual single embolus producing a variable cortical hemorrhagic infarct in the closest comparable clinical situation.
Second, these experimental infarcts often encroached on the ventricular system, since they were often large in comparison to the total volume of brain. This made rupture into the ventricle more likely, whatever the instigating factor. Third, as we have demonstrated previously,10 dogs have an extremely generous collateral circulation to the brain in contrast to human beings. It is not easy to say whether this advantage in collateral circulation is beneficial or whether it may be harmful, in regard to hemorrhage within an infarct, when anticoagulants are added to the picture. Meyer11 has demonstrated experimentally that when heparin and Dicumarol are administered, the properties of the blood are such that it flows with less resistance in these small collateral channels. Thus more available collateral channels after occlusion conceivably could allow more access of blood to the region of the infarct. The last difference to be noted is that the cerebral arteries of the experimental animals were without atherosclerotic change. While this is in contrast to much of the clinical material with cerebrovascular disease, it is comparable to many clinical situations in regard to cerebral emboli.

The crux of this matter is a problem not directly related to any of the clinical indications for anticoagulants previously cited: that is, whether anticoagulants are helpful or harmful or neither in the immediate treatment of cerebral infarction. The experimental evidence we have presented herein points out that in this situation in dogs, anticoagulants are harmful. Clinical impressions from a limited number of cases would lead us to conclude that anticoagulant therapy in recently completed cerebral infarction does not favorably influence the natural history of the condition. However, neither have we been impressed by the amount of hemorrhage in the cerebral infarcts in such patients who have died as a result of their infarction. Recently, Carter12 has shown in a limited series that there was a statistical advantage in the use of anticoagulant therapy immediately after cerebral infarction from embolism. This advantage was in regard both to extent of recovery and survival. Also he noted that there was not unusual and extensive hemorrhage in the cerebral infarcts of the 7 patients who failed to survive after such anticoagulant therapy.

When we examine our evidence in regard to all the cerebral infarcts from the clot fragments, we find additional data. Of all such animals which survived longer than 2 days, that is, with exclusion of the period of high mortality from the infarct alone, there were 37 control dogs; there were also 37 dogs which received anticoagulants either before or after the infarction. All of the control animals survived the full period of observation. There were 4 deaths in the group which received anticoagulants. Two of these deaths were associated with gross intracerebral and intraventricular hemorrhage, and 2 deaths were related to massive gastrointestinal bleeding. In neither of the latter 2 dogs was there unusual bleeding in cerebral infarcts, even though infarcts were large (fig. 3, bottom). In all 4 dogs which died, the prothrombin activity had dropped to less than 5 per cent, that is, the dogs had received excessive anticoagulant therapy.

Our experimental evidence presents the antagonist's point of view in regard to the use of anticoagulants immediately after completed cerebral infarction. However, we do not consider that the evidence precludes the desirability of further clinical investigation of potential benefit from properly administered anticoagulant therapy in recently completed cerebral infarction, particularly infarction from embolism.

Summary

Cerebral infarction has been produced by intracarotid injection of either liquid vinyl acetate or 48-hour-old autologous clot fragments. With either method, the administration of anticoagulants increased the hemorrhagic component of the infarcts. This increase was less apparent in the infarcts produced by clot fragments since these are relatively hemorrhagic infarcts even without anticoagulants. Preinfarction anticoagulants
appeared to give some protection in terms of total amount of cerebral infarction after injecting clot fragments. Postinfarction anticoagulants did not give this protection. The evidence cited here regarding increased hemorrhage in completed cerebral infarcts with anticoagulant therapy does not necessarily militate against the use of this treatment in certain well-defined categories of cerebrovascular disease.

**Summario in Interlingua**
Infarcimento cerebral esseva producite per le injection intracarotidie de (1) liquide acetato vinylie o (2) autologe fragmentos de coagulo de un etate de 48 horas. In ambe casos, le administration de anticoagulantes augmentava le componento hemorrhagie del infarcimentos. Isti augmento esseva minus apparente in le caso del infarcimentos producite per fragmentos de coagulo, proque istos es relativamente hemorrhagie mesmo sin anticoagulantes. Le administration de anticoagulantes ante le production del infarcimentos pareva provider un certo grado de protection, a judicar per le amonta total de infarcimento cerebral trovate post le injection de fragmentos de coagulo. Anticoagulantes administrate post le production del infarcimentos non provideva un tal protection. Le hic-reportate observationes con respecto a augmentos de hemorrhagia in complete infarcimentos cerebral resultante de terapia anticoagulante non representa necessarimente un argumento contra le uso de iste tractamento in certe ben-definite categorias de morbo cerebro-vascular.

**References**
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