The Clotting Action of Russell Viper Venom

By Samuel I. Rapaport, Knut Aas and Paul A. Owren

The demonstration of the thromboplastin-like activity of Russell viper venom by Macfarlane and Barnett was followed by its use in some laboratories as a substitute for brain thromboplastin in "prothrombin time" determinations. However, it gradually became apparent that there were important differences between the "thromboplastic" activity of Russell viper venom and that of brain thromboplastins. These include: (1) the failure of venom to accelerate the clotting of plasma from which all platelet and lipoid material has been removed, and the variation in the venom clotting time which may be produced by alteration of the platelet and/or lipoid content of plasma,

(2) the very rapid clotting times of 4 to 8 seconds obtained with venom-lipoid combinations, compared to the 12 to 15 second clotting range of most tissue thromboplastins, (3) the failure of venom when substituted for brain thromboplastin in "prothrombin time" determinations to measure the full effect of dicumarol administration, (4) the inability of the lipid anti-thromboplastin described by Tocantins and Carroll to inhibit the activity of venom in contrast to its striking inhibition of tissue thromboplastins and (5) the failure of the clotting time obtained with venom to reflect the changes produced in plasma by contact with a foreign surface such as glass.

Saline extracts of brain seem to provide the equivalent in thromboplastic activity of the combined effect of 3 thromboplastic components of the blood: platelet-lipoid factor, antihemophilic factor A (antihemophilic globulin) and antihemophilic factor B (PTC, Christmas factor). Thus the addition of brain thromboplastin to the plasma of a patient with thrombocytopenia, hemophilia A, or hemophilia B will give a normal "prothrombin time". There is good evidence, however, for the belief that the brain thromboplastin does not act directly upon prothrombin but reacts first with the plasma factor, proconvertin (plasma precursor of SPCA, plasma precursor of Factor VII, co-thromboplastin) to form a new and more powerful activity, which has been called convertin because it is believed to initiate the conversion of prothrombin to thrombin. In our opinion, the 12 to 14 second normal brain thromboplastin "prothrombin time" is due in large part to the time required for this initial reaction between thromboplastin and proconvertin. Pre-incubation of brain thromboplastin with proconvertin in the presence of calcium will shorten the clotting time markedly. In contrast, when brain thromboplastin is added to proconvertin deficient plasma, a very long clotting time is obtained.

It has been stated recently that the coagulant action of Russell viper venom is similar to that of brain thromboplastin in that both require proconvertin (factor VII) and proaccelerin (factor V) for their full effect. However, it seemed to us that all of the above listed differences between venom and brain thromboplastin could be explained if venom acted independently of the proconvertin

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content of the plasma. Venom would clot rapidly, then, hemophilia A plasma, hemophilia B plasma, and proconvertin deficient plasma. Venom plus platelet-lipoid factor would be equal to the effect of tissue thromboplastin plus proconvertin or of convertin.

The experiments presented below support this hypothesis. They demonstrate that the clotting action of venom-lipoid is independent of the proconvertin content of the plasma but not of its proaccelerin content. Thus, they explain why Russell viper venom is unsatisfactory as a thromboplastic agent for use in the control of dicumarol therapy. They also provide the basis for a simple test to differentiate hypoproconvertinemia from hypoprothrombinemia and proaccelerin deficiency.

MATERIALS AND METHODS

Normal Plasmas

Nine volumes of venous blood were collected in glass or silicone coated tubes containing 1 volume of 0.1 molar sodium citrate solution. Platelet rich plasma was obtained by centrifugation at 900 r.p.m. for thirty minutes. Platelet poor plasma was obtained by centrifugation at 2,500 r.p.m. for thirty-five minutes or at 12,000 r.p.m. for twenty minutes. Glass activated plasma was prepared by adding approximately 1 volume of fine quartz glass powder to 4 volumes of platelet poor plasma. The plasma was shaken frequently for fifteen minutes at room temperature and the glass powder was then removed by centrifugation at 2,500 r.p.m. for 5 minutes.

Pathological Plasmas

Proconvertin deficient plasma was obtained from two patients with a congenital deficiency of this factor. Citrated plasma was stored in small lots at -20 C. and defrosted as needed. The clotting behavior of this plasma has been described in detail elsewhere.13 The plasma has a normal content of prothrombin and proaccelerin but only about 1 per cent proconvertin. Proaccelerin deficient plasma was prepared from a patient with parahemophilia13 in whose plasma no proaccelerin can be demonstrated. It was also available as citrated frozen plasma which was defrosted as needed. Hemophilia A plasma was prepared from a patient with the classical clinical findings of severe hemophilia whose clotting defect was corrected by barium sulfate adsorbed oxalated human plasma, asbestos filtered ox plasma, and hemophilia B plasma. Hemophilia B plasma was prepared from a patient who also exhibited the classical clinical findings of severe hemophilia but whose clotting defect was corrected by old stored serum, by the citrate eluate obtained from the barium sulfate adsorbent and by hemophilia A plasma.

Russell Viper Venom

The Burroughs Wellcome Co. preparation “Stypven” was used. A 1/10,000 solution of venom was made in (1) the distilled water diluent furnished in the package, (2) a 1 per cent dilution of cream in buffer, (3) a 2.2 Gm. per cent suspension of crude cephalin in buffer, and (4) a 0.07 Gm. per cent suspension of crude cephalin in buffer.

Crude Cephalin

This material is the acetone insoluble, ether soluble fraction of human brain prepared according to the directions of Milstone.14 Two hundred grams of human brain so treated yielded about 4 grams of a creamy, waxy material. This was suspended in 100 ml. of buffer and centrifuged to remove the coarse particles. The supernatant consisted of a 2.2 Gm. per cent suspension of fine milky material which was stored at -20 C. and could be thawed and refrozen several times without apparent loss of activity. This material was also diluted 1 part to 29 parts of buffer to give a 0.07 Gm. per cent suspension.
Saline Brain Thromboplastin

A saline-buffer extract of human brain was prepared by a technic previously described.\(^\text{15}\)

Adsorbed Ox Plasma

Citrated ox plasma was passed through a 50 per cent asbestos filter. Details of this technic have been published earlier.\(^\text{19}\) Such plasma contains proaccelerin, antihemophilic factor A, and fibrinogen but is free of significant amounts of proconvertin and antihemophilic factor B. It contains small amounts of prothrombin. Therefore, for the specific prothrombin determinations and for its use with viper venom, a second adsorption for 10 minutes with 100 mg. of barium sulfate (Baker) per ml. of plasma was made.

Veronal Buffer

A modified veronal buffer (pH 7.35, \(\mu 0.154\)) was made by mixing sodium diethylbarbiturate 11.75 Gm., sodium chloride 14.67 Gm., 0.1 N hydrochloric acid 430 ml. and distilled water to 2000 ml.

Diluting Solution

Diluting fluid for the 1/10 dilution of plasma in the various systems consisted of 177 ml. of 0.034 M sodium citrate, 200 ml. of veronal buffer and physiological saline to make 1000 ml.

Calcium Solution

The optimal concentration was obtained for each test system. It was usually 0.030 M CaCl\(_2\).

RESULTS AND DISCUSSION

The variation in the venom clotting time which may be produced by change of the platelet and/or lipoid content of the same sample of fasting normal plasma is illustrated by the following experiment. The clotting times of platelet rich and platelet poor plasma were determined when 0.2 ml. of each plasma was added to 0.2 ml. of different “thromboplastin” mixtures and, after 3 to 5 minutes incubation at 37 C., clotting was initiated by the addition of 0.2 ml. of calcium chloride. These data are given in table 1. In this and subsequent tables, the clotting times are given in seconds and are the averages of at least two determinations. One can see that there was no significant difference between the clotting times of platelet rich and platelet poor plasma when a saline extract of brain was used as the thromboplastin as in the usual Quick test. However, when Russell viper venom dissolved in the distilled water diluent provided in the package was used, a striking difference was found between the clotting times of the two

<table>
<thead>
<tr>
<th>Thromboplastic agent</th>
<th>Type of plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline brain thromb.</td>
<td>Platelet rich</td>
</tr>
<tr>
<td>Viper venom in dist. water</td>
<td>11.0</td>
</tr>
<tr>
<td>Viper venom in 1% cream</td>
<td>15.0</td>
</tr>
<tr>
<td>Viper venom in 2.2% cephalin</td>
<td>20.5</td>
</tr>
<tr>
<td>Viper venom in 0.07% cephalin</td>
<td>7.5</td>
</tr>
<tr>
<td>Viper venom in 0.07% cephalin</td>
<td>4.5</td>
</tr>
</tbody>
</table>
plasma samples. The venom dissolved in a 1 per cent suspension of cream in buffer gave even longer times and the difference between platelet rich and platelet poor samples persisted. This was surprising since a 1 per cent suspension of cream is one of the sources of lipoid suggested for use with the venom. However, when the venom was dissolved in a 2.2 per cent suspension of crude cephalin, there was a pronounced shortening of the clotting time to the 7 to 8 second range for both plasma samples. Solution of the venom in a 0.07 per cent suspension of cephalin gave even faster times in the 4 to 5 second range. These very rapid times have never been obtained on human plasmas with tissue thromboplastin, but have been obtained by us in the past on the addition of preformed convertin to recalcified plasma.

These results confirm the necessity for providing a constant optimum amount of lipoid material when Russell viper venom is to be used in clotting time determinations. That the more dilute cephalin suspension gave somewhat faster times than the more concentrated suspension is suggestive of the hypothesis of Macfarlane and Overman that there is an optimum ratio of lipoid to protein in thromboplastic material, alteration of which in either direction lessens its effectiveness.

However, the shortening of the venom clotting time with the 2.2 per cent cephalin suspension is of particular interest because it is in striking contrast to the lengthening of the clotting time produced by addition of the same strength cephalin suspension to clotting mixtures containing saline brain thromboplastin. This is shown in table 2 in which are listed the clotting times obtained in a system containing 0.2 ml. normal plasma, 0.2 ml. of 2.2 Gm. per cent cephalin suspension or buffer, 0.2 ml. brain thromboplastin or viper venom in water, and 0.2 ml. of calcium chloride.

The delay in the brain thromboplastin clotting time is due to the presence of a lipid anti-coagulant in the cephalin fraction. The properties of this anti-coagulant have been studied by Tocantins and Carroll who also first noted the immunity of Russell viper venom to its action. We have recently found that brain thromboplastin is also immune to the effect of the lipid inhibitor if the brain thromboplastin is incubated with serum in the presence of calcium for 1 minute before the lipid inhibitor is added. For example, if 0.1 ml. of aged serum, saline brain thromboplastin, and calcium chloride are incubated for 1 minute and then 0.1 ml. of cephalin and 0.1 ml. of plasma are added in rapid succession, coagulation occurs within ten seconds after the addition of the plasma. However, if the cephalin is included in the incubation mixture coagulation does not occur for 45 to 50 seconds after the addition of the plasma. The protection afforded the
thromboplastin by the preincubation with serum is due to the reaction of the thromboplastin with the proconvertin in the serum to form convertin. The lipid inhibitor is then unable to block the clotting action of the convertin.

This observation can explain the immunity of venom-lipoid to the action of the lipid inhibitor if venom-lipoid acts as convertin. Thus, an inhibitor which acts to block the reaction between tissue thromboplastin and proconvertin to form convertin would be powerless against a clotting agent which circumvents this reaction and was instead the equivalent of preformed convertin.

It has long been known that contact of blood with glass or other negatively charged surfaces promotes clotting not only by causing disintegration of platelets but by a change in a plasma clotting component as well. This increase in the coagulability of the plasma has been variously attributed to the removal of an anti-cephalin,\textsuperscript{10} to the removal of a prothrombin inhibitor,\textsuperscript{20} to the activation of prothrombinogen,\textsuperscript{21} and of thromboplastinogen,\textsuperscript{22} and to the activation of the “Christmas factor.”\textsuperscript{23} The effect of glass contact can be demonstrated in the absence of added thromboplastic material as in the recalcification of platelet free plasma, when a partial thromboplastin such as dilute cephalin suspension is added to plasma, and also in the presence of a strong saline brain thromboplastin. However, as Tocantins has pointed out,\textsuperscript{16} it cannot be demonstrated when Russell viper venom is used as the clotting agent.

This is shown in table 3 which gives the Quick clotting times for a normal, platelet-poor plasma, one portion of which had been exposed only to silicone surfaces even to the final determination of the clotting time, and the other portion of which had been activated by shaking with fine quartz glass powder after the platelets had been removed.

The failure of the venom to reflect the increased coagulability produced by the glass contact can also be explained by the independence of the coagulant effect of venom from the proconvertin content of plasma, for we have found\textsuperscript{24} that the shaking of fresh plasma for a few minutes with fine quartz glass powder will increase not only anti-hemophilic B factor activity but also proconvertin activity, the latter as much as 400 per cent when tested in the specific proconvertin system of Owren and Aas.\textsuperscript{16} Such an exposure to a large glass surface area apparently accomplishes in a few minutes the same activation of proconvertin as has been shown previously\textsuperscript{25} to occur on permitting plasma to stand for several days in glass tubes. Brain thromboplastin, which must react first with proconvertin, will measure this increased proconvertin activity by such shortening of the clotting time as is seen in table 3. Viper venom, which circumvents the thromboplastin-proconvertin reaction, shows no shortening, but instead a very slight

\begin{table}[h]
\centering
\caption{The Different Effect of Activation of Plasma by Glass Powder on Brain Thromboplastin and Viper Venom Clotting Times}
\begin{tabular}{l|c|c}
\hline
Thromboplastic agent & Type of plasma & \\
& Silicone plasma & Glass activated plasma \\
\hline
Saline brain thromb. & 16.5 & 11.0 \\
Viper venom in dist. water & 9.5 & 10.5 \\
\hline
\end{tabular}
\end{table}
Table 4.—A Comparison of the Brain Thromboplastin and Viper Venom Clotting Times of Plasma Defective in Different Clotting Factors

<table>
<thead>
<tr>
<th>Type of plasma</th>
<th>Thromboplastic agent</th>
<th>Saline brain thromb.</th>
<th>Viper venom in 0.07% cephalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>12.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Hemo. A</td>
<td></td>
<td>10.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Hemo. B</td>
<td></td>
<td>11.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Hypoproconvertinemia</td>
<td></td>
<td>53.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Parahemophilia</td>
<td></td>
<td>64.0</td>
<td>40.0</td>
</tr>
</tbody>
</table>

lengthening of the clotting time due to the adsorption of a small amount of prothrombin on the glass.

If, then, venom-lipoid supplies to plasma the equivalent of convertin activity, rapid clotting times should be obtained not only on the addition of venom lipoid to hemophilia A and hemophilia B plasma but on its addition to hypoproconvertinemia plasma also. Table 4 lists the clotting times obtained when first brain thromboplastin and then Russell viper venom in 0.07 per cent cephalin suspension are used in a Quick system with different plasmas each congenitally defective in one plasma clotting factor.

It is seen that venom-lipoid is able to clot in about 5 seconds plasma defective in every component tested except proaccelerin. Convertin, also, is known to be ineffective in the absence of proaccelerin. The difference between the very long clotting time of hypoproconvertinemia plasma with brain thromboplastin and its very rapid coagulation by venom-lipoid is clearcut evidence that venom-lipoid does not require proconvertin to be an effective clotting agent.

This finding explains why the use of venom as a thromboplastic agent for Quick "prothrombin time" determinations on patients on dicumarol therapy can lead to serious accidents for dicumarol and the newer dicumarol, like anticoagulants, depress not only prothrombin formation but proconvertin formation as well. Very often the latter is depressed much more than the former. With viper venom, only the lowering of the prothrombin content is measured. The depression of proconvertin is unseen.

This can be demonstrated by doing parallel determinations of the prothrombin-proconvertin time (P.-P. time), prothrombin time, proconvertin time, and viper venom clotting time on plasmas from patients on dicumarol or phenylindandione therapy. The principles and methods for the first 3 of these determinations have been described in detail previously. In brief, the P.-P. time is obtained by mixing 0.2 ml. of a 1/10 dilution of test plasma with 0.2 ml. adsorbed ox plasma, 0.2 ml. of brain thromboplastin and 0.2 ml. of calcium chloride. Every known clotting factor is in excess except for prothrombin and proconvertin, whose content in the test plasma is measured. The specific proconvertin system has been modified from that previously described in that plasma from a patient with congenital hypoproconvertinemia is used. This system consists of 0.2 ml. of hypoproconvertinemia plasma (supplies prothrombin in excess), 0.2 ml. of adsorbed ox plasma (supplies proaccelerin in excess), 0.2 ml. of a 1/10 dilution

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TABLE 5.—The Parallel Determination of P.-P. Time, Proconvertin Time, Prothrombin Time and Viper Venom Time on Dicumarol and Phenylindandione Plasmas, Given as Percentage of Normal

<table>
<thead>
<tr>
<th>Sample</th>
<th>P.-P.%</th>
<th>Proconvertin %</th>
<th>Prothrombin %</th>
<th>Viper venom %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>1</td>
<td>122</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>18</td>
<td>42</td>
<td>36</td>
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<tr>
<td>6</td>
<td>10</td>
<td>2</td>
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<td>68</td>
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<tr>
<td>8</td>
<td>18</td>
<td>3</td>
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<tr>
<td>9</td>
<td>45</td>
<td>54</td>
<td>80</td>
<td>64</td>
</tr>
</tbody>
</table>

of the test plasma, 0.2 ml. of brain thromboplastin and 0.2 ml. of calcium chloride. The clotting time then reflects the proconvertin content of the test plasma. The specific prothrombin time is determined by mixing 0.2 ml. of especially prepared serum (supplies proconvertin in excess), 0.2 ml. of ox plasma which is adsorbed a second time with barium sulfate to remove the last traces of prothrombin (supplies proaccelerin in excess), 0.2 ml. of a 1/10 dilution of the test plasma, 0.2 ml. of brain thromboplastin, and 0.2 ml. of calcium chloride. Variation in the clotting time of this system will depend only upon the prothrombin content of the test plasma.

The viper venom system was set up exactly as the P.-P. system except that again the ox plasma was adsorbed a second time to remove the last traces of prothrombin and a 1/10,000 solution of venom in 0.07 per cent cephalin suspension was used as the “thromboplastin”. Dilution curves made by determining the clotting time of various dilutions of normal plasma gave straight lines when plotted on log-log paper with a clotting time of 11 seconds for 100 per cent plasma and 45 seconds for 15 per cent plasma.

The results of these determinations are given in table 5 as percentage of normal. Sample number 1 is from a patient with congenital hypoproconvertinemia. The remaining samples are dicumarol or phenylindandione plasmas. These data confirm that a clotting system using viper venom measures only the prothrombin content of the plasma. Differences in the values for prothrombin by the specific prothrombin method and by the viper venom method are within the range of error of the methods. These results explain why Mawson found a poor correlation between one-stage and two-stage methods for prothrombin in dicumarol plasma when brain thromboplastin was used in the one-stage method, but a good correlation when Russell viper venom was used. The data from samples 6 and 8 reveal again the dangers inherent in the use of the venom time alone for following the effect of dicumarol or dicumarol-like anti-coagulant therapy.

CONCLUSIONS

The experiments cited above clearly demonstrate that Russell viper venom in the presence of platelet-lipoid factor possesses a clotting activity equivalent
to that of convertin. It is able to clot normal plasma, hemophilia A and hemophilia B plasma, and congenital hypoproconvertinemia plasma within 5 seconds. Like convertin, it is not able to clot proaccelerin deficient plasma rapidly.

These facts form the basis for a rapid presumptive test for hypoproconvertinemia, which is simply to do a Quick “prothrombin time” determination first with the usual brain thromboplastin and then with Russell viper venom. Proconvertin deficient plasma will give a prolonged Quick clotting time with brain thromboplastin but a normal time with viper venom. In contrast, prothrombin or proaccelerin deficient plasma will give a prolonged clotting time with both agents. If the blood to be tested is centrifuged at slow speed so that the majority of platelets are left in the plasma, it will be unnecessary to add lipoid material to the viper venom for this test. The venom can be made up in the diluent provided in the package.

When a 1/10,000 solution of venom is 0.07 per cent cephalin suspension is substituted for brain thromboplastin in the P. and P. system, the system becomes a sensitive quantitative one stage measure of prothrombin alone and can be used as a substitute for the specific prothrombin system of Owen and Aas. When this is done, though, care should be taken that the last traces of prothrombin are removed from the adsorbed ox plasma proaccelerin reagent.

This analysis of the clotting action of viper venom explains the differences between this material and brain thromboplastin cited in the introduction. Thus the venom alone, which supplies the equivalent of the combination of anti-hemophilic factor A, antihemophilic factor B, and proconvertin, will not function in the absence of the platelet-lipoid factor. Unlike tissue thromboplastin which contains the platelet-lipoid factor, the effectiveness of venom as a clotting agent will vary with the platelet-lipoid content of the clotting mixture until an optimum ratio of venom to lipoid is attained.

The difference between the 12 to 14 second Quick clotting times obtained with brain thromboplastins and the 4 to 5 second times with venom-lipoid is due to the fact that the former must first undergo a time consuming reaction with proconvertin to form convertin, whereas the latter, like convertin, can begin prothrombin conversion immediately. The inability of the lipid anti-thromboplastin of Tocantins and Carroll to inhibit viper venom is likewise explained for this inhibitor has been shown to be ineffective against convertin. The failure of viper venom to reflect the change produced in plasma by glass contact can also be understood because glass contact activates proconvertin. Finally, the failure of viper venom to measure the full effect of dicumarol administration is explained since the venom will measure only the change in the prothrombin content of the plasma but not that of the proconvertin.

**Summary**

1. It has been shown that Russell viper venom in the presence of lipoid cofactor can clot hemophilia A plasma, hemophilia B plasma and proconvertin deficient plasma within 5 seconds. It is unable to clot proaccelerin deficient plasma rapidly. Thus the clotting behavior of venom-lipoid is similar to convertin.

2. A rapid presumptive test for hypoproconvertinemia is simply to do a Quick
clotting time with brain thromboplastin and then with viper venom. Proconvertin deficient plasma will give a prolonged brain thromboplastin time but a normal venom time. Prothrombin or proaccelerin deficient plasma will give long clotting times with both agents.

3. The observation that Russell viper venom acts independently of the proconvertin content of plasma explains the differences between the venom and brain thromboplastins. It also explains the failure of venom to measure the full effect of dicumarol administration.

**SUMMARIO IN INTERLINGUA**

(1) Nos ha demonstrate que le veneno del vipera de Russell es capace—in le presentia de co-factor lipoide—a coagular intra 5 secundas plasma a hemophilia A, plasma a hemophilia B, e plasma deficiente in proconvertina. Le veneno non es capace a producir un rapide coagulation in plasma deficiente in proacelerina. Assi le activitate coagulative de iste combination de veneno plus lipoide es simile a illo de convertina.

(2) Un simple e rapidissime modo de executar un essayo presumptive pro hypoproconvertinemia consiste in executar un test de Quick con thromboplastina cerebral e un altere con veneno del vipera de Russell. Plasma deficiente in proconvertina resultara in un tempore prolongate in le test con thromboplastina cerebral sed in un tempore normal in le test con veneno. In le caso de plasma deficiente in prothombina o proacelerina ambe agentes resultara in longe tempores coagulative.

(3) Le observation que le activitate del veneno del vipera de Russell es independente del contento de proconvertina in le plasma explica proque le veneno non pote mesurar le effecto complete del administration de dicumarol.

**BIBLIOGRAPHY**


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