Influence of Some Vasoactive Drugs on Fibrinolytic Activity

By Murray Weiner, M.D., Kurt de Crinis, M.D., Walter Redisch, M.D. and J. Murray Steele, M.D.

With the technical assistance of Louis G. Weisberg, B.S., and Gordon R. Gilbert, B.S.

The phenomenon of fibrinolysis in thromboembolic disease is of great importance. In this communication the authors present striking evidence of fibrinolysis induced by drugs.

A RECENTLY published tabulation of simple organic compounds reported to induce some weak fibrinolytic activity includes only compounds known to influence vasomotion (procaine, epinephrine, diethylaminoethanol). Studies in our laboratory concerning the influence of vasomotor drugs on the clotting mechanism have resulted in the observation that intravenously administered nicotinic acid induces rather strong fibrinolytic activity. This paper presents data on the influence of representative vasomotor drugs on the clotting mechanism, and particularly on fibrinolysis.

METHODS

Rates of peripheral blood flow were measured in man in a constant temperature-constant humidity room by methods previously described. Clotting tests included 1-stage prothrombin time (whole and diluted plasma), recalcification time, antithrombin activity and fibrinolytic activity, both by test tube observation and the coagulograph (“thromboelastograph” of Hartert). Drugs studied in man included nicotinic acid (orally, intravenously, intramuscularly, and intraarterially), nicotinamide (intravenously), calcium gluconate (intravenously), diethylaminoethanol (intravenously), histamine (intravenously), papaverine (intravenously and intra-arterially) and ilidar (intra-arterially).

RESULTS

Nicotinic Acid. In no experiment was there a significant alteration in any of the clotting tests performed except fibrinolysis. Following a single intravenous dose of nicotinic acid in man, marked fibrinolytic activity was noted, both by test tube observation and the coagulograph. The nicotinic acid flush was maximal during the period of injection. Fibrinolysis was not evident until several minutes after completion of the injection. Nicotinic acid in doses of 10 to 100 mg. was injected intravenously in 13 experiments, intra-arterially in 3, and intramuscularly in 2. In 17 of the 18 experiments, distinct fibrinolytic activity was noted without any significant alteration in the prothrombin complex as measured by a 1-stage technic, recalcification time, antithrombin activity, or heparin tolerance. Fibrinolytic activity was usually maximal about 5 to 20 minutes after injection and then became less intense but occasionally was still detectable after 1 to 2 hours. Figure 1 presents the coagulographs of 6 experiments in the same subject. Larger intravenous doses resulted not only in more rapid completion of lysis 20 minutes after injection but also in persistent lysis 1 hour after dosage. In 2 instances, the double-curve phenomenon on the coagulograph previously reported by Von Kaulia was noted. The effect on blood flow to the lower extremity was studied in 6 of the intravenous and in the 3 intra-arterial experiments. In all 6 intravenous experiments, increases of flow rate were recorded, ranging from 64 to 290 per cent of the control values. In the 3 intra-arterial experiments, the flow rate increased by 250 and 97 per cent in 2, and decreased slightly in 1. All 3 showed distinct fibrinolysis.
The in vitro addition of nicotinic acid to plasma in concentrations of 0.05 to 500 mg./L. failed to induce any fibrinolytic activity. Oral administration of single doses of from 100 to 300 mg. in 11 subjects did not result in fibrinolysis in any of the experiments. In most instances, there was a distinct flush 10 to 20 minutes after oral administration, indicating that the drug was absorbed. The chronic oral administration of daily doses of 300 to 6,200 mg. for periods of from 1 to 25 weeks in 4 subjects also failed to yield any evidence of lysis.

The intravenous administration of nicotinic acid to dogs, guinea pigs, and rabbits failed to result in fibrinolysis as judged by the technics described.

*Nicotinamide*. Since this substance has the same antipellagra activity as nicotinic acid (and is believed to be the essential form of this vitamin in important enzyme-cofactor systems), but is not vasoactive, its fibrinolytic effect was studied. Three of the subjects who had demonstrated marked fibrinolysis following nicotinic acid were given an identical dose of nicotinamide intravenously. No fibrinolytic phenomena resulted.

*Calcium Gluconate*. Since the intravenous injection of this substance results in a flush similar to that following nicotinic acid, its effect on the clot was observed in 3 subjects. There was no evidence of fibrinolytic activity.

*Histamine*. Three patients given 3 mg. intra-arterially were observed to develop significant increases in blood flow rate (table 1) but failed to show any altered fibrinolytic activity.

*Papaverine*. This drug was administered intravenously in 2 experiments, and intra-arterially in 1 in doses of 30 to 45 mg., resulting in a distinct increase in rate of blood flow in the extremity. There was no activation of fibrinolysis.

*Ilidar*. In 3 experiments, 50 mg. infused intra-arterially resulted in an increase in blood flow in all instances. No fibrinolysis was induced.

*Diethylaminoethanol*. Although marked increase in blood flow was observed in all of 3 experiments, in only 1 was some weak fibrinolytic activity observed.

**DISCUSSION**

The capacity of parenterally administered nicotinic acid to induce fibrinolytic activity in vivo in man has been demonstrated. The mechanism of this phenomenon and the reason for its failure to develop in other species remain obscure. The absorption of orally administered nicotinic acid in man is well established and was confirmed in these studies by the observation of the flush in many subjects. Nevertheless, even the largest oral dose employed failed to induce fibrinolysis.

Since intravenously administered nicotinamide failed to activate fibrinolysis and also had no vasomotor activity, a relationship between vasodilatation and fibrinolytic activity was suspected. Nicotinic acid influences the superficial skin capillary bed as is evidenced by the flush. Contrary to common belief, this flush phenomenon is not necessarily accompanied by an elevation in skin temperature or a measurable increase in blood flow rate. Nicotinic acid does, however, affect the rate of blood flow to the lower limb, not correlated in time with the flush phenomenon. It was,
**TABLE 1.—Effect of Vasomotor Drugs on Fibrinolytic Activity**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of administration</th>
<th>Number of experiments</th>
<th>Coagulograph</th>
<th>Test tube</th>
<th>Average per cent increase in blood flow rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic acid*</td>
<td>10 to 100 mg.</td>
<td>I.V.</td>
<td>13</td>
<td>Lysis in 12</td>
<td>Lysis in all</td>
<td>117</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>100 mg.</td>
<td>I.V.</td>
<td>3</td>
<td>No lysis</td>
<td>No lysis</td>
<td>—</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>10 ml. of 10% solution</td>
<td>I.V.</td>
<td>3</td>
<td>No lysis</td>
<td>No lysis</td>
<td>—</td>
</tr>
<tr>
<td>Histamine</td>
<td>3 mg.</td>
<td>I.A.</td>
<td>3</td>
<td>No lysis</td>
<td>No lysis</td>
<td>144</td>
</tr>
<tr>
<td>Papaverine</td>
<td>45 mg.</td>
<td>I.V.</td>
<td>2</td>
<td>No lysis</td>
<td>No lysis</td>
<td>94</td>
</tr>
<tr>
<td>Ilidar</td>
<td>50 mg. in 200 ml. infusion</td>
<td>I.A.</td>
<td>3</td>
<td>No lysis</td>
<td>No lysis</td>
<td>110</td>
</tr>
<tr>
<td>Diethylamino-ethanol</td>
<td>50 ml. of 10% solution</td>
<td>I.A.</td>
<td>1</td>
<td>No lysis</td>
<td>No lysis</td>
<td>143</td>
</tr>
</tbody>
</table>

*Tabulation includes only patients who had not previously received nicotinic acid by other routes.

therefore, thought necessary to look for a nicotinic acid-like fibrinolytic effect of other flush-inducing drugs as well as of drugs that increase rate of blood flow to a limb in the manner of nicotinic acid. Calcium gluconate, histamine, papaverine, and Ilidar all failed to induce fibrinolysis.

Experiments currently in progress indicate that orally administered nicotinic acid not only fails to induce fibrinolysis, but may alter the usual fibrinolytic response to subsequent intravenous doses.

**SUMMARY**

Parenterally administered nicotinic acid induces fibrinolytic activity in man. This response does not occur with a variety of other drugs capable of increasing rate of peripheral blood flow. Oral nicotinic acid and parenteral nicotinamide fail to induce fibrinolysis.

**SUMMARIO IN INTERLINGUA**

Acido nicotinic, administrate per via parenteral, induc activitate fibrinolytic in humanos. Iste responsa non occurre con un varietate de altere drogas capace a accelerar le fluxo de sanguine peripheric. Acido nicotinic per via oral e nicotinamindo per via parenteral non induce fibrinolyse.

**REFERENCES**

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Data are presented on 30 healthy individuals aged 5½ to 45 years who sustained cerebrovascular accidents. The 2 large categories of strokes in the young were venous and arterial thrombosis. In healthy women, puerperal hemiplegia was the most common form of spontaneous stroke. It was characterized by the sudden onset of headache, convulsions, hemiplegia, or other focal neurologic signs during a previously healthy puerperal period. The episode occurred several hours to several weeks postpartum and was caused by cortical venous thrombosis. Twelve patients were reported with recovery in all, although minor neurologic sequelae persisted in 3 patients. Two other patients had similar findings during pregnancy; these were also thought to be caused by venous thrombosis. Arterial occlusion was thought to be the cause of strokes in the 16 other patients. Involvement of the carotid artery was often seen in strokes in the young. The cardinal sign of thrombosis of this vessel was hemiplegia. Contralateral headache was often present. Horner’s syndrome and homonymous hemianopsia were frequent ocular signs of carotid artery thrombosis. The difficulty in distinguishing between middle cerebral and carotid artery thrombosis was discussed. Carotid arteriography was not recommended as a diagnostic procedure because of the hazard of precipitating or exacerbating a hemiplegia in an already susceptible patient. The cause of thrombosis in these patients was thought to be a solitary atheromatous plaque. No specific treatment was recommended, since prognosis is good in these patients.

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