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Anticoagulants and Fibrinolytics

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Introduction

THE HISTORY of clinical medicine contains a wealth of information on the discovery and introduction of new drugs. Some of them – antibiotics and many neuroleptics, among others – were quickly assimilated into the day-to-day practice of physicians, since their efficacy was immediately evident and confirmed. Other drugs, however, suffered a different fate.

The upsurge in treating patients and the seemingly brilliant therapeutic results were followed by disappointment and doubts as to the efficacy of many drugs. These so-called drugs of the year disappeared from clinical use, and only published articles remind us of the hasty conclusions drawn by certain authors. The list of such drugs is indeed long, and includes a whole series of "coronary vasodilators" (amplivix, khellin, and others), drugs for treating ulcers and oncological diseases, and so on.

The fact that these drugs and the methods of treatment based on their use, lacking a therapeutic effect, passed into oblivion was largely due to the insufficient pathogenetic foundation for such therapy. Today it is difficult to speak about the radical treatment of atherosclerosis with linethol or diosponin, since the underlying mechanisms of this disease remain unclear. Similarly, the difficulty of treating a spasm of heart vessels is due to the absence of a clear-cut understanding of that pathologic state.

There is no doubt as to the effect of anticoagulants and fibrinolytic drugs on the mechanism of thrombus formation. If the blood clotting factors in blood are reduced with the aid of anticoagulants, then the possibility of fibrin filaments falling out, and simultaneously the possibility of thrombus formation, is substantially reduced. The use of fibrinolytics is based on the same pathogenetic foundation.

By promoting the destruction of fibrin filaments with the help

of such preparations, it is possible to act upon the main link of thrombofibrin formation and, as a result, to prevent thrombogenesis or even cause absorption of the thrombus. The latter is possible only during the early stages of clot formation.

In spite of the apparent simplicity of the theory, even today scientists at numerous conferences and symposia continue to discuss the efficacy and expediency of using these preparations. Although the preventive and therapeutic methods have been in use for a long period of time, the practicing physician's opinion of them has not fully crystallized. So far, there are no clear-cut indications for the use of anticoagulant and fibrinolytic therapy, nor are there precise recommendations concerning dosage and duration of treatment. This uncertainty can be explained from two points of view. The first proceeds from the multiplicity of factors involved in thrombus formation. Numerous factors can play an important role, namely, the condition of the vascular walls, the velocity of the bloodstream, the content of coagulating factors, the state of anticoagulating mechanisms, and the cellular link of hemostasis, among others. At the moment, it is difficult to single out which of these components plays the primary role in the formation of any given thrombus.

The general trends in changes of blood clotting factors and anticoagulating mechanisms can be judged only indirectly. However, there are indications that the general tendencies in the state of biochemical indicators of thrombogenetic properties of blood do not always reflect local changes in a particular area of the vessels. Changes in the vascular wall, the state of local blood circulation, and even disturbed coagulating and fibrinolytic properties of blood in the area of thrombus formation may occur even with quite satisfactory indices of general homeostasis.

Even when therapy is directed toward one of the thrombogenetic factors, there is no absolute certainty that it will act on the main mechanism of thrombus formation under local conditions. Moreover, the entire problem of thrombosis should not be narrowed down to biochemical changes. Local changes in the vessel and its surface, the electric potential, and local blood circulatory disorders may contribute to the thrombus formation.

Under these conditions, anticoagulant and fibrinolytic thera-

py sharply reduces the potential possibility of thrombogenesis, including several links in the pathogenesis of its emergence. In the majority of cases, a reduction in the content of clotting factors or destruction of fibrin creates conditions for prevention of lysis or a thrombus.

The second element that should be taken into account when evaluating the effect of anticoagulants and fibrinolytics is the difficulty in proving their efficacy. In addition, numerous other factors come into play, restricting the action of anticoagulants and fibrinolytics and thereby diminishing their effect. One such factor is the lifetime of a thrombus. The irreversible changes of fibrin occurring during thrombus formation may progress so far that neither anticoagulants nor fibrinolytics can affect the thrombus.

There are still other theoretically founded limitations on the action of these substances.

Recent years have witnessed significant changes in our understanding of hemostasis regulation. New anticoagulants and fibrinolytics have been obtained; in fact, the very pattern of therapy has undergone substantial changes. It is by no means easy for a practicing physician to find his way through the deluge of recommendations and proposals and to properly evaluate the results of discussions. Quite often, it is difficult to pinpoint the criteria according to which a particular drug is prescribed, the efficacy indices of the drug, and the appropriate dosage and duration of treatment. Finally, changes in the coagulating and fibrinolytic properties of blood during treatment are quite complicated.

Anticoagulant and fibrinolytic therapy requires the physician to take a sober-minded and attentive approach to each patient. Numerous treatment failures have been connected with a standardized approach to the prescription of these drugs. Individual prescriptions, with due consideration for all the peculiarities of the patient's organism and, most important, the state of the coagulating and fibrinolytic properties of the patient's blood, have determined the success of treatment with these drugs. Diagnosis and treatment should be based on scientific methods, precise knowledge of the mechanisms of development of the pathologic process, and the mechanism of action of the drugs.

This question, of late, has received exceptionally great atten-

tion in the literature. New information has surfaced about drugs for regulating hemostasis and for prevention and treatment of thromboembolic diseases. Much of this information was not included in previously published manuals. In view of this, we feel the time has come to summarize the information on anticoagulants and fibrinolytics in accordance with up-to-date achievements in the study of hemostasis.

This book represents an attempt to briefly compare contemporary concepts about the pharmacology of anticoagulants and fibrinolytics and their antagonists with the possibility of clinical application and efficacy in prevention and treatment of thromboembolic conditions. Besides the drugs which are firmly established in practical medicine, it is expedient to evaluate those groups of substances which are still in the developmental stage but bear promise for the pharmacologic regulation of hemostasis. The chapters dealing with this may be of particular interest to investigators who have launched a purposeful quest for new drugs in this field of experimental and clinical pharmacology.

It was not our objective to offer the reader information on the mechanism of blood coagulation. This has been well elucidated in previous publications.

This book focuses primarily on the properties and methods of employing pharmacologic substances that regulate the given function. The great number of publications on the topic have compelled us to make selected references to works published at different times and to describe only certain drugs displaying an anticoagulating and fibrinolytic effect.

As we offer our presentation to the American reader, we fully realize that there are definite differences in the approach to therapy with anticoagulants and fibrinolytic enzymes in the United States and the Soviet Union. First and foremost, such differences are related to the broader application of these drugs in Soviet clinics for the treatment or prevention of thromboses and, in particular, myocardial infarction. Back in 1963, one of the authors reported to the Institute of Heart, Lungs, and Blood the good results that had been obtained in the treatment of myocardial infarction with fibrinolytic enzymes. Since then, the Soviet Union has amassed considerable experience indicating that early (up to three to four hours after onset) administration

of these drugs restricts and diminishes the zone of necrosis and improves the course of the disease.

In part, these data have emerged because the Soviet Union has a special emergency aid service that ensures early hospitalization of patients with thromboses and myocardial infarction in cardiologic institutes. We hope that this experience may be of interest and of some use to our American colleagues. In addition, we suggest protocols for the use of antithrombotic drugs by specialists in other countries; generic synonyms are also presented.

The requirements which we place before fibrinolytic enzymes led to the development of a new class of drugs, the so-called immobilizing enzymes, which ensure a high stability of fibrinolytic enzymes in the blood and a lesser incidence of side effects.

At present, the USSR Cardiological Center and the American firm, Abbott Laboratories (North Chicago), are involved in a collaborative effort to develop immobilized urokinase, which we hope will open up new vistas in the treatment of thromboses and myocardial infarction.

We feel it necessary to underscore the second distinguishing feature of the use of anticoagulants and fibrinolytics in the Soviet Union, namely, their extensive preventive application in cardiologic and obstetric-gynecologic clinics and in certain diseases related to dysfunctions of immune complexes. For example, the use of heparin during the so-called preinfarction period reduces the incidence of infarcts. The administration of anticoagulants in myocardial infarction reduces over twofold the incidence of thromboembolic complications.

One thing is certain: further efforts in developing anticoagulant and fibrinolytic therapy by scientists in the United States, the Soviet Union, and other countries will lead to the discovery of new, more effective drugs for the prevention and treatment of thrombotic complications.

PART I

ANTICOAGULANTS

FROM THE POINT OF VIEW of practical medicine, anticoagulants comprise those drugs which reduce clotting of blood. The name of this group of drugs derives from the term "anticoagulantia" (from the Greek *anti*, meaning "against," and the Latin *coagulans, coagulantis*, meaning "promoting or inducing curdling").

Anticoagulants are used mainly in experimental and clinical medicine to prevent thrombogenesis and thromboembolic complications, as well as to arrest the further development and growth of thrombi once they have appeared. In the latter case, conditions are created for dissolving the fibrinous clot due to endogenous or administered fibrinolytic enzymes, as well as that due to nonenzymic lysis, as was demonstrated by Kudryashov (1975) and by Kudryashov and Lyapin (1978).

Anticoagulants may be divided into several groups on the basis of their chemical structure, mechanism of action, and onset and duration of effects. Such a division is, of course, somewhat arbitrary and not universally accepted. Nevertheless, to simplify the presentation of material this classification will be followed.

1 / Anticoagulants of Direct, Swift Action

THIS GROUP OF ANTICOAGULANTS includes heparin and heparinoids that are similar in structure and mode of action to heparin, and hirudin and hirudinoids that are similar in structure and effect to hirudin. These substances reduce coagulation of blood both in the human organism and in the test tube. Of all the direct-acting anticoagulants used in medical practice, heparin has had the broadest application and thus is given major consideration in this chapter. Other groups of direct-acting anticoagulants will be dealt with more briefly.

HEPARIN

Discovery and Production

The name stems from the word "hepar," meaning liver, from which it was isolated in the initial investigation. Today it is usually obtained from other sources. Heparin is a physiologic anticoagulant which is produced in the organism of man and animals. For medical use it is obtained from bovine tissue.

The anticlotting action of heparin was first observed by Pavlov. In experiments with a cardiopulmonary preparation, he noted that blood that had passed through this preparation did not coagulate for a long time. Blood coagulated more swiftly on exclusion of the lung cycle of circulation. On the basis of such observations, Pavlov as early as 1884 set forth the assumption that some kind of anticoagulation substance forms in the lungs and, on entering the bloodstream, noticeably retards clotting.

Somewhat later, Shmidt, the founder of the enzyme theory of blood coagulation, working at Yurievsk University, managed to isolate an anticoagulating substance from liver. However, these theories of Pavlov and Shmidt were not developed further at the time and did not lead to the isolation of a purified anticoagulant.

This was achieved later on. While studying thromboplastin of tissue origin, Howell (1912) suggested that the acting trigger of thromboplastin is a phosphatide with properties analogous to those of cephalin. Proceeding from this, he gave his pupil, McLean, a medical student at Johns Hopkins University, an assignment to determine whether the thromboplastic action is related to pure cephalin or to admixtures.

In his experiments McLean (1916), in addition to pursuing that investigation, studied the thromboplastic properties of phosphatides isolated from liver, brain, and heart (lecithin, sphingomyelin, cuorin). During the chemical processing of phosphatides from liver, he isolated a fraction that had pronounced inhibitory effect on blood coagulation.

These researchers devoted great attention to the rediscovered substance and, together with their fellow workers, launched an in-depth study of the properties of the new anticoagulant. Later, they reported on the results of their work. The substance prevented blood coagulation in vivo and in vitro in minimal concentrations for several hours. Injections of the anticoagulant into animals did not increase arterial pressure or change the heart rate or breathing.

Among the methods initially used for obtaining the substance, by far the easiest was isolation from liver, although in principle it could also be obtained from heart tissue, skeletal muscles, lymphatic nodes, and even from the mucous membrane of the uterus. In 1918 Howell and Holt described the properties of the substance in greater detail and named it heparin in view of the large quantities found in liver and because an anticoagulant was isolated from it.

Howell subsequently improved the method of extracting heparin and in 1928 described its chemistry and physiology. It was realized that the substance could be physiologically significant. Consequently, the author regarded heparin as a physiologic anticoagulant, but one which might be used as a medication.

The first commercial preparation was released for experimental study on the basis of these data. The production of a crystalline heparin made it possible to come closer to determining the chemical structure of the substance and pinpointing its physiochemical properties. Remarkably successful investigations in

that direction were conducted, beginning in the 1930s, by Jorpes (1946–1962) in Stockholm. The results that he obtained enabled researchers in different countries to continue extensive studies of the new anticoagulant and to use it in clinical practice. A summary of the history of the discovery and production of heparin was submitted by McLean in 1959.

In several countries today heparin is produced in pure form from animal tissue, in particular with the aid of additional semisynthetic processing. All this has made it possible to return once again to specifying the chemical structure of the substance, its physiologic and pharmacologic properties, although an exact description must await the results of further investigation.

Biological Synthesis and Physiologic Significance of Heparin in the Organism

As was subsequently established, heparin forms in the basophilic granules of mast cells in different organs and tissues, where it accumulates together with histamine. There are, however, reports that heparin has been detected in lower animals in which mast cells were not found.

The investigation of color reactions on heparin's structure promoted the identification and quantitative evaluation of heparin in biological substrates. For instance, it was found that in tissue ethers with a high molecular weight, methylene blue produces a red metachromatic color. Jorpes (1946) undertook similar investigations and established that the addition of toluidine blue to heparin produces a violet color.

Further, with the help of histochemical methods it was illustrated that granules in Ehrlich-type mast cells contain heparin that passes from the mast cells into interstitial space and the blood. Such cells were named "heparinocytes." Granules of these cells yield a metachromatic color when stained with toluidine blue. It is this color reaction that is extensively employed for chemical and histochemical identification of heparin in tissues and other substrates.

Confirmation of the role of mast cells in biological synthesis and the deposition of heparin in mast cells was the result of numerous subsequent observations. A great number of pieces of evidence, direct and indirect, were introduced to prove this. It was noted that there was a definite correlation between the