Clinical aspects of the therapeutic effect on the complement system human

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SUMMARY

The search for new drugs of natural origin with fundamentally different mechanisms of action is due to the limited effectiveness of drugs created by chemical synthesis. Induction of a cascade of reactions of the complement system refers to one of the central links of innate immunity, which promotes the activation of leukocytes, facilitates phagocytosis of microbes, and is also directly involved in the elimination of extracellular pathogens. Purified human C1-esterase inhibitor (C1I) in high doses has organoprotective and anti-inflammatory effects. The work uses a fundamentally new way of studying the mechanism of action of drugs, which has certain prospects in the study of the mechanisms of action of drugs of natural origin.

Key words: complement system, C1-esterase inhibitor, sepsis, natural medicines.

One of the promising areas of modern pharmacology is the study of the mechanism of action of drugs (drugs) of natural origin, including those obtained using biotechnology, and homeopathic preparations.

The search for new drugs of natural origin with fundamentally different mechanisms of action is due to the limited effectiveness of drugs created by chemical synthesis. This is evidenced by epidemiological data indicating the absence of positive changes in the level and structure of mortality in the population over the past decades. One of these areas is the search for new therapeutic targets and approaches to the pharmacotherapy of diseases, in the pathogenesis of which the complement-associated inflammatory response plays a significant role. The preparation of C1-esterase inhibitor is a lyophilisate obtained by deep processing of blood plasma of healthy donors.

The biological significance of complement as an inflammatory mediator

The complement represents the most ancient defense system, evolutionarily entrenched among invertebrates and mammals,

designed to maintain homeostasis. This system, consisting of 30 blood plasma proteins, by triggering a cascade of catalytic reactions, provides a full biological response of the body when exposed to a variety of stimuli. Complement is one of the key links in the pathogenesis of the inflammatory response that develops in both infectious and non-infectious diseases. The accumulated volume of experimental and clinical data indicates that at a certain stage, the inflammatory response loses its protective value. So, uncontrolled inflammation is the main cause of the development of septic shock and infectious pathology. At the same time, initially adapted cellular and molecular structures become sensitive to the activated complex of proteins of the complement system. In recent years, the hypothesis about the role of the microbial factor and the systemic inflammatory response in the development of multiple organ disorders in chronic heart failure has been confirmed [1]. In the pathogenesis of coronary heart disease, an important place belongs to such phenomena as tissue hypoxia, accumulation of under-oxidized products, release of biologically active mediators, activation of complement, which stimulate the development of a local inflammatory reaction.

Uncontrolled activity of the complement system within both local and systemic inflammatory response has a negative clinical significance. For example, blocking the biological effects of C3 and C5 components contributed to a decrease in the number of lethal complications in animals [2]. The increased concentration of C3a significantly correlates with the mortality rate in patients with sepsis and / or septic shock [3]. It is assumed that the activated C5a component of the complement system plays a dominant role in the pathophysiology of the septic process, since it significantly exceeds C3a in biological activity [4]. It is also known that the C5 subunit of the complement system can induce hypotension and leukopenia, the synthesis of such cytokines as TNF-α, IL-6 and IL-1 by monocytes [5, 6]. Up to 20% of cases of miscarriage are associated with hypocomplementemia and protein deposition on the placenta [7]. Hereditary deficiency of an endogenous inhibitor of the complement system (C1-esterase inhibitor (C1I)) may manifest as spontaneous generalized edema of the body [8].

The biological role of C1-esterase inhibitor

C1I is an acute phase protein related to plasma serine protease inhibitors. C1I is the main inhibitor of the classical pathway of the complement system, an indirect inhibitor of the kallikrein-kinin, coagulation and fibrinolytic systems. The concentration of C1I in the blood of a healthy person is about 250 mg / ml, which corresponds to 1ME [9, 10]. Several types of cells are involved in the synthesis of this acute phase protein, including hepatocytes, fibroblasts, and endothelial cells [11]. The synthesis of C1I is stimulated by IFNγ, TNF-α, IL-6, IFN-α. [12, 13, 14].

C1I is characterized by a variety of effects, among which should be highlighted:

• Suppression of the activated complement system leads to a decrease in formation of C5a;

• Inhibition of the contact system leads to a decrease in concentration factor XII, precallikrein, bradykin;

• Decrease in the concentration of inflammatory mediators in plasma (TNF-α, IL-10, IL-6, IL-8);

• Direct binding of lipopolysaccharide and inhibition of its interaction with LPS binding protein;

• Inhibition of the adhesive properties of activated leukocytes;

• Increase the bactericidal activity of neutrophils and improve bacterial clearance.

C1I, like most proteins of the serpin family, can be inactivated by elastase released by neutrophils [15]. Despite the fact that in conditions of an inflammatory reaction, an increase in the level of C1I in the blood is characteristic, a high level of protein consumption and direct inactivation create the prerequisites for deficiency states.

Results of studies of C1-esterase inhibitor in cardiologyThe activation of the complement system within the inflammatory response develops within a few hours after early reperfusion of the ischemic myocardium [16]. At the same time, with prolonged myocardial ischemia, the peak of activation of the complement system can be observed in a few days [17, 18]. The complement system plays a leading role in stimulating neutrophil activity, accumulating free radicals, and inducing endothelial dysfunction. It is assumed that the local accumulation of the terminal complex of the complement system and anaphylatoxins can lead to a violation of the contractile function of the myocardium [19].

In 2001 Horstick et al. published data indicating that intravenous infusion of a C1-esterase inhibitor at a dose of 40 U / kg 10 minutes before coronary reperfusion significantly reduced the area of myocardial damage in pigs (the area of damage in the main group - 44.1 ± 13.8% , placebo - 76.7 ± 4.6%; $p < 0.05$) caused by 120-minute occlusion of the left descending coronary artery. The protective effect of the C1-esterase inhibitor was accompanied by a decrease in the concentration of CPK and troponin in the group of animals treated with the drug [20].

The first report on the use of a C1-esterase inhibitor as a “despair” therapy for emergency surgical myocardial revascularization after ineffective coronary angioplasty appeared in 1998. In the early postoperative period, 3 patients showed signs of unstable hemodynamics, despite high doses of vasopressors and the use of a balloon counterpulsator. Prescription of a C1-esterase inhibitor (at a dose of 4000 U) led to stabilization of hemodynamics within 6–8 hours, withdrawal of vasopressors and restoration of inotropic myocardial function [21].

In 2002, data from the first prospective controlled study of the efficacy and safety of C1-esterase

inhibitor in acute myocardial infarction. In 16 people who received early thrombolytic therapy and C1-esterase inhibitor (the drug was prescribed immediately after successful revascularization), an early decrease in troponin-T and MV-CPK to normal values and lower AUC values (38% and 57%) were achieved compared with the control group (n = 18), in which only thrombolysis was performed. The study noted good tolerance of the C1-esterase inhibitor, including in the group receiving 100 U / kg IV bolus followed by a maintenance dose of 2.0 U / kg / hour for 48 hours.

The results of a double-blind, placebo-controlled study confirmed the cardioprotective effect of C1I in patients undergoing emergency coronary artery bypass grafting due to ST-segment elevation myocardial infarction (STEMI). Thus, in patients who received 1000 IU C1I immediately before surgery, compared with placebo, there was a low need for inotropes (p = 0.001), early stabilization of blood pressure (p = 0.03) and an increase in cardiac index (p = 0.02). , there was a shorter time spent in the ICU (p = 0.04) and in the hospital (p = 0.03). Troponin I levels were also significantly lower after reperfusion [22].

Thus, it is possible to identify the main directions of the use of the C1-esterase inhibitor - preliminary administration of the drug before procedures aimed at myocardial revascularization, as a prophylaxis of possible reperfusion disorders; therapy aimed at reducing the zone of necrosis in acute myocardial infarction; as an adjuvant for the correction of hemodynamic disorders arising from myocardial revascularization.

Results of studies of C1-esterase inhibitor in sepsis

In MMA them. THEM. Sechenov, an experimental study was carried out to study the pharmacological activity of a C1-esterase inhibitor (Bitsizar®, OOO "Biogenius", Russia, Moscow). It has been shown that the administration of an exogenous human purified C1-esterase inhibitor leads to a significant increase in animal survival against the background of the introduction of a potentially lethal dose of LPS; and also contributes to the stabilization of clinical and laboratory parameters reflecting the degree of activation of the systemic inflammatory response upon administration of a lethal dose of LPS [23]. In an open prospective study of the efficacy and safety of the C1-esterase inhibitor drug, work was continued on studying the properties of C1I in patients with sepsis. The objects of the study were patients (n = 20) with a verified diagnosis of sepsis within 48 hours from the onset of clinical symptoms, who received C1I in the form of intravenous infusions in a total dose of 12000 IU for 2 days. Infusion of Bitsisar was accompanied by a significant increase in C1I activity. The increase in C1I activity in the first 10 hours from the moment of administration reached 71.25% (33.6-160.95%). It was also noted that the main pharmacokinetic parameters are directly related to the severity of systemic inflammation in patients with sepsis. The obtained T1 / 2 values (236.2 h (93.2–236.3 h)) turned out to be higher than those previously described for healthy volunteers [24]. System depletion Infusion of Bitsisar was accompanied by a significant increase in C1I activity. The increase in C1I activity in the first 10 hours from the moment of administration reached 71.25% (33.6-160.95%). It was also noted that the main pharmacokinetic parameters are directly related to the severity of systemic inflammation in patients with sepsis. The obtained T1 / 2 values (236.2 h (93.2–236.3 h)) turned out to be higher than those previously described for healthy volunteers [24]. System depletion Infusion of Bitsisar was accompanied by a significant increase in C1I activity. The increase in C1I activity in the first 10 hours from the moment of administration reached 71.25% (33.6-160.95%). It was also noted that the main pharmacokinetic parameters are directly related to the severity of systemic inflammation in patients with sepsis. The obtained T1 / 2 values (236.2 h (93.2–236.3 h)) turned out to be higher than those previously described for healthy volunteers [24]. System depletion

of complement as a result of increased consumption indicated a decrease in C4, C3 and C1I values at the beginning of the study before drug administration, observed in the framework of an uncontrolled systemic inflammatory response. The analysis of 28-day mortality, assessed using the Kaplan-Meier method, showed a tendency to an increase in survival in the group of patients receiving S1I (Fig. 3). In the study group, mortality was 10%, while in the control group (n = 22) - 36% (p = 0.09, Log Rank Mantel-Cox). Against the background of ongoing therapy in patients of the main group who received the drug Bitsisar, the concentration of C-reactive protein significantly (p = 0.03) decreased by the 3rd day of the study compared with patients from the control group.

Evaluation of the efficacy and safety of parenteral administration of C1I in patients admitted to intensive care units with a diagnosis of sepsis or septic shock served as the goal of a double-blind, randomized, placebo-controlled study by Caliezi et al [25]. The results of this study confirmed the safety of early administration of high doses of C1I (12,000 IU within 48 hours), and also revealed a positive effect of the drug on the rate of recovery of renal function in patients with sepsis. In a study by Zeerleder et al. (2003) demonstrated a significant decrease in the concentration of circulating elastase α1-antitrypsin complex, which is a potent neutrophil activator in sepsis, against the background of the administration of C1I to patients with severe sepsis or septic shock in a total dose of 12,000 IU [26].

The studies carried out make it possible to distinguish a number of C1I effects observed in sepsis:

• Increased expression of C1I antigen;

• Decrease in the activity of the complement system (decrease in the concentration of C4v / s, increase in the level of C3 and C4);

• Decrease in the concentration of creatinine, blood serum urea;

• Reducing the need for vasopressors;

• Decrease in the concentration of elastase-α1-antitrypsin complex;

• Reducing the manifestations of the syndrome of increased capillary permeability. The accumulated material allows one to judge about the high therapeutic potential of C1I in patients suffering from various pathologies. Continuing the study of the clinical features of C1I drugs within the framework of the concept of evidence-based medicine is necessary to increase the reliability of the existing data.

The proposed ways of studying the mechanism of action of a C1-esterase inhibitor can be used in the study of drugs of natural origin, including the objectification of the effectiveness of therapeutic agents of traditional medicine.

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