THE USE OF HEPARIN IN THE TREATMENT OF ACUTE PANCREATITIS

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The pancreas is the second largest glandular organ of the gastrointestinal tract, responsible for producing digestive enzymes and endogenous hormones (insulin, glucagon, somatostatin, pancreatic polypeptide).

Acute pancreatitis (AP) was first described by Bonetus in the 17th century. As medicine developed, next centuries brought new descriptions and studies of this disease. Especially the last decades saw major changes also in pathogenesis theories, and consequently, in the principles of therapeutic management of the disease.

Acute pancreatitis is a disease of varying severity. The disease can be of mild severity. In such a case, the symptoms include intensive pain, nausea and vomiting, or the pain alone, and the course of this type is characterised by spontaneous recovery. In some cases, the disease leads to severe pancreatic damage with concomitant multiorgan damage, often leading to death. In this population of patients many multiorgan disorders occur (involving not only the pancreas), including clotting disorders. The use of heparin in the treatment of acute pancreatitis (at first aimed at improving microcirculation) has received wider attention, since it resulted in reduction of leukocytosis and increase in oxygen partial pressure (1). These findings were confirmed in clinical studies in rats. Further interest in the mechanisms for development and treatment of pancreatitis resulted in several interesting clinical papers, which evaluated, among other things, the effect of heparin on development of acute pancreatitis following retrograde cholangiopancreatography. At first, the study results were ambiguous, e.g. Rabenstein et al. found no positive effect of heparins; however, more recent studies confirm the positive effect of heparin treatment on the course of this disease (2, 3). Multicentre studies conducted in China revealed decreased mortality as well as a lower Balthazar score.

DISCUSSION

Acute pancreatitis

Acute pancreatitis is an acute inflammatory process in the gland associated with premature activation of pancreatic enzymes, and it can be accompanied by damage to near and distant tissues and organs. At present, commonly accepted is the classification of acute
pancreatitis proposed in 1992 in Atlanta, with modifications of 2000 (4). The accepted classification of acute pancreatitis includes the mild type characterised by minimal (or non-existent) organ damage, well responding to the treatment and the severe type characterised by a severe course with multiorgan damage.

Many etiopathogenetic factors of acute pancreatitis were found (among other things: alcohol, choledocholithiasis, medicines and infectious diseases). The exact mechanism leading to pancreatic cellular damage is different depending on the etiological factor, and sometimes not fully understood. However, the common feature of all types of AP is the role of trypsin. As a result of disturbances in granular segregation in follicular cells, zymogen granules combine with lysosomes. This leads to intracellular activation of trypsinogen. Active enzymes trigger a destructive process of cellular damage and lead to activation of numerous pro-inflammatory factors, the kinin system as well as the complement system. Pro-inflammatory factors taking part in this process, especially TNF-α, IL-1, IL-6 and IL-18, cause the anti-inflammatory barrier (IL-2, IL-4, IL-10 and IL-1Ra) to break, leading to further development of the process, initially limited to the pancreas (5).

Therapeutic management depends on numerous factors, including etiology, severity of the disease process and concomitant diseases. The severity of the disease process is usually assessed using point scales evaluating biochemical parameters; commonly used are the Ranson scale, Glasgow scale or APACHE II scale as well as the complement system. Pro-inflammatory factors taking part in this process, especially TNF-α, IL-1, IL-6 and IL-18, cause the anti-inflammatory barrier (IL-2, IL-4, IL-10 and IL-1Ra) to break, leading to further development of the process, initially limited to the pancreas (5).

In the recent years, the principles of therapeutic management of acute pancreatitis have changed. Thanks to both clinical and experimental studies, we have gained a better understanding of the pathological mechanisms in acute pancreatitis. This has resulted in a change in the approach towards the therapeutic principles. Commonly used starvation has been replaced with rational principles of both enteral and parenteral nutrition. Medicines that were commonly used in the near past, such as apronitin, have lost their importance. However, in spite of numerous studies conducted, the problem of effective treatment of acute pancreatitis remains open (6).

In the course of severe AP, disseminated intravascular coagulation is a frequent occurrence, and this condition is commonly treated with heparin with successful outcomes. During studies on hyperlipidaemia in acute pancreatitis conducted as early as in the 1960s, the positive effect of heparin was noted (7, 8).

**Heparin**

Heparin was discovered by Jay McLean nearly 100 years ago (in liver cells, which is reflected in the name), but its mechanism of action is still an object of interest to many researchers (9). In the literature, there is an increasing volume of reports on the possibility of using heparin in the treatment of acute pancreatitis. We know that microcirculation disorders present in the course of pancreatitis contribute to the progression of the inflammatory process, both in the pancreas and in other organs. That is why an attempt was made at using heparin, initially mainly to improve microcirculation.

Heparin, a member of the group of glycosaminoglycans, exhibits an anticoagulant effect after binding with antithrombin III; thrombin production is inhibited by accelerated factor Xa degradation. Moreover, heparin inhibits the activity of thrombin as well as of coagulation factors IX, X, XI and XII (serine proteases). It also indirectly affects factors V and VIII. Heparin molecules, through binding to the surface of the endothelium, increase its negative potential, thus hindering adherence. Another known mechanism of action of heparin depends upon heparin cofactor II (HC II). This
is the protein with which low molecular weight heparin binds. Heparin also affects platelets, by increasing their aggregation or inhibiting their function; this process depends on the concentration of heparin (3, 4).

The effect of heparin on the course of the inflammatory process is currently well documented. Anti-inflammatory action is associated with the above anticoagulant mechanisms that are directly related with the course of inflammation. The inflammatory process activates the coagulation system and leukocytes, which release a tissue-activating factor (endothelial clotting). The ongoing coagulation process affects the further course of inflammation through a positive feedback mechanism. The presence of active factors VII and X stimulates protease-activated receptors, increasing the concentration of adhesion factors. This mechanism leads to a further exacerbation of vascular endothelial damage, clotting and inflammation (10, 11).
demonstrate that prophylactic use of heparin significantly decreased the risk of pancreatitis following endoscopic cholangiography (p = 0.07) (23). A multicentre study, conducted by Lu XS, concerning pancreatitis of severe type (unfortunately in a small number of patients) documented that small doses of low molecular weight heparins of 2500–5000 iu resulted in mortality reduction (p < 0.05–0.01) and in improved Balthazar score (p < 0.05) (18). As in other studies using similar doses, no increased risk of haemolytic complications was found. The authors of the cited paper recommend introducing low molecular weight heparin into the treatment of severe pancreatitis, as an effective, safe and easy therapeutic option.

SUMMARY

The presented data on the action of heparin, both unfractionated and low molecular weight, confirm its beneficial action in severe acute pancreatitis. Taking into account the inductive action of trypsin on the course of acute pancreatitis, the use of inhibitive properties of heparin towards serine proteases seems a natural choice of treatment. Furthermore, owing to lipoprotein lipase activation, the serum level of triglycerides is reduced. Low molecular weight heparins, owing to their common availability, ease of use and the fact that they do not require constant monitoring of the coagulation system during treatment, can be a beneficial option of acute pancreatitis treatment.

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