PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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The mechanism of actions of Octreotide, Bupleurum-Peony Cheng Qi decoction and Dan Shan in severe acute pancretitis

WU Xie-Ning

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The pathogenesis of severe acute pancreatitis (necrotizing pancreatitis) is comp licated and has not been elucidated up to date. In my opinion, it is multifactorial, and aggressive treatment should be directed to the mutifaceted pathophysiology[1]. A cumulative series of twenty cases were treated with the regimen i .e., combined traditional Chinese and modern medicine. No death, almost no morbi dity and no serious complications, such as ARDS and DIC occurred, only mental co nfusion as sequela occurred in a patient with previous cerebral infarction. The present article is to discuss the mechanism of actions of the medicins used in this treatment regimen.

THE PATHOGENESIS OF SEVERE ACUTE PANCREATITIS

It involves ① the release of pancreatic and lysosomal enzymes by the pancreatic acini which induce pancreatic autodigestion; ② the increase of vascular permeability, resulting in microcirculatory impairment; and ③ overstimulation of macrophages and neutrophils with release of many cytokines, inflammatory mediators (leukotrienes, prostaglandins, platelet activating factor) and free radicals. These factors interact with one another producing pancreatic acinar damage and intestinal epithelial barrier dysfunction. If not corrected instantly, it might lead to gut barrier damage and translocation of intestinal bacteria and endotoxin, resulting in a "second attack" caused by infection and endotoxemia, producing multiorgan dysfunction syndrome and eventually multiorgan failture.

Severe acute pancreatitis is most frequently precipitated by gallstone, biliary sludge, microlithiasis with or without bile reflux, obstruction of biliary-pancreatic common pathway, high fat anf high protein diet, alcohol consumption and ischemia here in Shanghai, hence, I think it is multifactorial and multifaceted a disease. The detailed mechnism will be delineated in another paper.

OCTREOTIDE AND SOMATOSTATIN

On reviewing the medical literature, octreotide and somatostatin are found to act on many facets. Either of them inhibits cholecystokinin which stimulates the synthesis, secretion and release of pancreatic enzymes[2], concomitantly it also stimulates and activates the monocytic-macrophagic system, lower the end otoxin level in acute necrotizing pancreatitis[3]. An experimental study showed that somatostatin could cause the blockage of endotoxin, IL-1, IL-6, IL-2, TNF-α and restore them to a near normal level[4]. Microcirculatory impairment is the initiating as well as aggravating factor in necrotizing pancreatitis, octreotide could decrease the small intestinal and colonic blood flow, and cause redistribution intrapancreatically, as well as decrease of the blood flow to the islets and to the cells secreting hormones with vasodilating property[5]. This is a very important point in contrast to the viewpoint that ortrotide decreased pancreatic blood flow in the past. Another experimental study also showed the pancreatic microcirculatory impairment mimiced the ischemia-reperf usion damage in humans, with impaired arteriolar perfusion, increased vascular permeability and aggregation and stasis of neutrophils in the postcapillary venules. Via the mediation of the adhesive molecules on the vascular endothelium, the neutrophils interacted with the endothelial cells, the oxygen free radicals pro duced by the neutrophils damaged the vascular endothelium, resulted in endothelial swelling, making the capillary lumen narrowed and obstructed, and the functional capillary density decreased. By given octreotide, the changes in the postcapillary venules were much lessened as compared with those not given octrotide, the statistical difference was significant[6]. No adhesion of neutrophils in the

Department of Gastroenterology, Shanghai First People's Hospital, Shang hai 200080, China

Dr. WU Xie-Ning, Professor of Medicine, B.S., M.D. Editor of Ten books on Hepatology and Gastroenterology, having 185 papers published.

Correspondence to: Dr. WU Xie-Ning, Department of Gastroenterology and Central Research Laboratory, Shanghai First People's Hospital, No. 85, Wujing Road, Shanghai 200080, China
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postcapillary venules were seen, indicating that octreotide attenuated the interaction between neutrophils and endothelial cells, thus provideding a protective effect. Octreotide also increased PGI_2 level[7], inhibited the synthesis of vasoconstricting leukotrienes and decreased the eicosanoid products[6]. Basing on the above facts, octreotide or somatostatin is a requisite in the treatment of severe acute pancreatitis.

BUPLEURIUM-PEONY CHENG QI DECOCTION

The herbal mixture Bupleurium-Peony Cheng Qi decoction has seven constituents: *Bupleurum*, *White peony*, *Scutellaria*, *Rhubarb* (*Rhei Rhizome*), *Unripe bitter orange*, *Magnolia bark*, *Refined mirabilite*. This herbal mixture also acts on multifacets of the disease, among which, rhubarb is the major constituent[8]. It inhibits the secretion and activity of the pancreatic enzymes, such as trypsin, lipase, phospholipase A2, chymotrypsin, elastase, amylase, kallikren -kinin and is synergistic with octrotide (or somatostatin) in this aspect. It stabilizes the lysosomal membrane of acinar cells [9], which is important in attenuating the acinar damage. It inhibits the inflammatory cytokines, its ant hracene derivative inhibits the phagocytic function of phagocytes, thereby inhibiting their overstimulation. As it is known, cytokines, such as IL-6, IL-1, IL-8 and TNF-α, are released by overstimulation of macrophages. A recent experimental study showed that acute phase proteins were induced by IL-6 and inhibited by rhubarb. Furthermore, the neutrophilic infiltration was only minimal in the necrotizing pancreatitis rats. The chemotactic effect of neutrophils on the inflamed area was by IL-8. Rhubarb can neutralize and expel the endotoxin, resulting in low blood endotoxin level with subsequent low release of TNF-α, these are the indirect evidences of rhubarb's inhibitory effect on cytokine release[4]. Rhubarb also inhibits vascular permeability, after oral administration, rhubarb is more concentrated in the pancreas, liver and kidney, whereas the brain and the lung are the next, and inhibition of the vascular permeability can cause cessation of exudation in the above organs and tissues. This is crucial in the prevention of local complications of the pancreas itself as well as prevention of leakage of fluid into the peritoneal cavity which causes peritonitis, hypovolemia and hypoalbuminemia, adult respiratory distress syndrome (ARDS) and pancreatic encephalopathy[5]. It also inhibits Na^+, K^+ATPase, impedes the transport of Na^+ from intestinal lumen into the cells and increases the volume of luminal contents, as the osmotic pressure increases within the colonic limen, intestinal wall is then stimulated and peristalsis increased. Concomitantly, the plasmaoncotic pressure increases, water switches to the blood circulation from the tissue. In this recipe, bupleurum and unripe bitter orange can increase the gastric emptying and small intestinal propulsion, refined mirabilite can also promote small intestinal peristatsis. As a whole, the herbal mixture restores the gut motility and absorptive function of the GI tract, relieving intestinal paresis and even paralysis. Magnolia bark and white peony relax the gut smooth musculature to restrain the overaction of the rest constituents. When the tongue becomes moistened, it indicates the gut function is restored[6]. Rhubarb has also broad-spectrum antibiotic action, *in vitro* it inhibits bacteroid fragilis, streptococci, B.Coli etc., neutraliges and expels the endotoxin in the intestinal limen. It of particular importance in the prevention of dislocation of intest inal bacteria and endotoxin [7]. It decreases blood lipids, inhibits prot ein catabolism, reduces urea synthesis and promotes urinary excretion of urea and creatinine[8]. Rhubarb has another important effect, i.e., a powerful relaxant of Oddi's sphincter, it can antagonize and abolish the contracting effect of octrotide, in favor of pancreatic fluid and bile drainage. This is of particular importance in the management of severe acute pancreatitis especially in cases with stone in the common bile duct. One of the precantions is that rhubarbcannot be decocted too long, i.e., two minutes is enough, otherwise many of its beneficial effects will be lost.

Bupleurum has transquilizing and analgesic effects, it also inhibits the growth of hemolytic streptococcus, staphylococcus aureus *in vitro*, also protects liver cells and decreases serum cholesterol and triglyceride, moreover, it enhances the intestinal contractility by acetylcholine. Another important effect is that it can stmulate the secretion of endogenous glucocorticoids[11] which can inhibit excessive secretion of cytokines and inflammatory mediators and protect acinar cells.

Unripe bitter orange has biphasic action on gut smooth muscle, low concentration stimulates, high concentration inhibits, which is dependent upon the functional status of the GI tract and the concentration of the herbal medicine. It has a synergistic effect on the GI musculature with bupleurum, refined mirabilite and rhubarb.

White peony inhibits amylase and has a weak relaxing effect on the Oddi's sphin cter.

Scutellaria has antibiotic effect on staphylococcus aureus, streptococcus, B.Coli, pseudomonas bacillus, etc. It decreases free fatty acid, triglyceride, serum and hepatic cholesterol and transaminase levels. High fat diet is often one of the precipitating factors of severe acute

pancreatitis, free fatty acid can cause lipoperoxidation and damage the vascular endothelium and acinar cells, and scutellaria inhibits lipoperoxidation both via vitamin C-Fe and NADPH-ADP routes. It can also inhibit release of histamine by mast cells, and the cyclo-oxygenase and lipo-oxygenase pathways which produce inflammatory mediators. Besides, it inhibits thromboxane A_2 synthase, reduces platelet aggregation and its adhesive function, promotes PGE_1 and PGE_2 levels, and transformation of fibrinogen to fibrin and prevents endotoxin induced disseminated intravascular coagulation (DIC). Finally, scutellaria also has the effect of lowering the elevated temperature.

SALVIA MILTIORRHIZA

Salvia Miltiorrhiza (Dan Shen) inhibits platelet aggregation, decreases blood viscosity, improves blood rheology and microcirculation, and inhibits the release of lysosomal enzymes and chemotacting neutrophils as well. Besides, it is an antioxidant as well as a calcium ion antagonist, the latter is also of great importance in improving the microcirculation. Experimental studies revealed that Ca^{2+} influx occurred via the acinar cell membrane before the exocrine pancreatic secretion started[13], and then some proteases were secreted. Ca^{2+} influx also occurred before the macrophages produced and released the cytokines such as TNF-α, IL-6 and IL-1. TNF-α is the crucial mediator of systemic complications, it upregulates adhesive molecules and induces excessive nitric oxide formation and superoxide free radicals, damaging the pancreas substance and other organs. Furthermore, it causes increased vascular permeability inducing microcirculartory ischemia. Calcium ion antagonist inhibits the release of TNF-α, improves the ischemia and increases the vascular perfusion, and it also inhibits the acinar cells to produce protease, ameliorating the inflammation and tissue damage. In our experience, Dan Shen is also an important therapeutic agent in the management of severe acute pancreatitis.

By and large, the above seven constituents of the herbal mixture have an overall effect on interruption of the cascade in severe acute pancreatitis. The herbal mixture restores the gut motility; inhibits release of cytokines and inflammatory mediators with subsequent attenuation of neutrophilic infiltration; improves pancreatic ischemia; prevents the dislocation of intestinal bacteria and endotoxin; and lowers blood lipoids, decreases lipoproxidation and reduces damages of vascular endothelium and acinar cell memdrane. Together with octreotide (or somatostatin) and Dan Shen, these would provide a synergistic as well as a complementary effect. During the treatment, the patients usually run a smooth course without fluctuation and recover uneventfully, hence, their combined use is of practical value and worth recommendation of wide use in clinical practice.

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