CONTROVERSIES IN MEDICINE: THE TREATMENT OF ACUTE PANCREATITIS

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SUMMARY

Oral food and fluid restriction and parenteral fluid substitution are unanimously accepted in the therapy of acute pancreatitis. Most other measures are controversial. The pros and contras of the modern therapeutical recommendations are discussed: gastric tube, antacids, atropine, cimetidine, glucagon, calcitonin, somatostatin, antienzymtherapy with aprotinin, and phospholipase A inhibition, therapeutic peritoneal lavage, improvement of microcirculation with dextrans and heparin, prophylaxis and therapy of complications, parenteral hyperalimentation, early surgical intervention with drainage or resection and endoscopic papillotomy for removal of bile duct stones in biliary acute pancreatitis.

RESUMO

Controvérsias em medicina. O tratamento da pancreatite aguda

A restrição oral de alimentos e a administração de soros por via parentérica, constituem medidas terapêuticas unanimemente aceites para a pancreatite aguda. Desenvolve-se e discutem-se as vantagens e desvantagens de algumas medidas terapêuticas, nomeadamente intubação naso-gástrica, antiácidos, atropina, cimetidina, glucagina, calcitonina, somatostatina, antienzimas — aprotinina e inibidores da fosfolipase A. A lavagem peritoneal terapêutica, a melhoria das condições de microcirculação com dextranos e heparina, a profilaxia e terapêutica das complicações bem como a hiper-alimentação parentérica, a intervenção cirúrgica precoce com drenagem ou ressecção e a papilotomia endoscópica para remoção da litíase do colédoco na pancreatite aguda de etiologia biliar, são, igualmente, avaliadas e discutidas.

Many measures in the treatment of acute pancreatitis are very controversial. This was obvious from inquiries in a large number of hospitals in West-Germany [35] and Austria.[7] The causes for these uncertainties are manifold. Most of the therapeutic recommendations are not based on controlled clinical trials but on empirical or pathophysiological findings. The course of acute pancreatitis depends on the aetiology, the severity at the beginning of the disease and the number of recurrences and is unpredictable. There have been efforts to develop prognostic criteria. Ranson et al [74, 76] defined biochemical parameters as being of prognostic value. In Germany a classification of acute pancreatitis in 3 gradings is widely used.[87] The letality in group I (mild edematous form) was found with 6 %, in group II (severe, hemorrhagic with partial necrosis) with 43 %, in group III (very severe with subtotal to total necrosis) with 80 % to 100 %. Gallstone-associated and idiopathic acute pancreatitis are said to have a higher letality (20 %) than the alcohol-associated form (7 %).[74] All these problems are contributing to the controversies about the treatment of acute pancreatitis.

1. MEASURES AGAINST THE INFLAMMATION AND AUTODIGESTION OF THE PANCREAS

Most of the measures which are in use aim at setting the gland at rest. This is possible on three levels: 1. Inhibition of gastric secretion and indirectly of the liberation of gastrointestinal hormones which stimulate the pancreas (Secreting, Cholecystokinin-Pancreozymin). 2. Inhibition of pancreatic secretion by blocking the ductular and acinar cells. 3. Inhibition of pancreatic secretion by action on cellular mechanisms.

1.1. Oral restriction of food and fluid. Gastric tube

Oral total restriction of food and fluid is generally accepted to be of help for the patient during the first days of an acute pancreatitis. Mainly it relieves the gastrointestinal tract and helps in treating paralytic ileus. Controlled trials do not exist. The use of a gastric tube has been the subject of three recent controlled studies.[26, 57, 66] They showed no decisive advantage; pain, nausea, fever, amylase etc. were not influenced by the gastric suction. On the other hand the patients studied had only mild atacks of acute pancreatitis and mostly were alcohol-associated. A surgical study[2] recently demonstrated that postoperatively a gastric tube was 10 times more often combined with pneumonia than in a control group without a tube. So it seems reasonable to conclude that in mild cases of acute pancreatitis a gastric tube is not obligatory but that it is of benefit for relief of the gastrointestinal tract in the more severe cases.

1.2. Antacids, cimetidine, atropine

Antacids are effective in buffering HCl in gastric juice, but at least an amount equivalent to 50 mEq every three hours must be used for this purpose. This is not reasonable

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in a situation where the GI-tract should be relieved from excess of fluid and therefore antacids are not recommended in acute pancreatitis. *Cimetidine* easily can be applied intravenously for blockade of acid production in the stomach. It has been studied in a double blind trial with 1200 mg/24 h in infusion over 4-5 days. Course and outcome of acute pancreatitis were significantly better with cimetidine than with placebo.[71] The letality in this study in both groups only was reported with 4 %, so the cases treated obviously were not very severe. Cimetidine does not influence pancreatic secretion.[28] Experimentally in the acute pancreatitis of rats it was found to worsen the state of the animals.[41, 47] In human alcoholic acute pancreatitis in a controlled study the course was not altered but the amylase activity in the serum was found to be significantly higher with cimetidine.[62] Three cases have been published with acute pancreatitis during therapy with cimetidine.[3, 97] At present good evidences is not available that cimetidine damages the pancreas. So it should be applied in cases where gastrointestinal bleeding under intensive care is feared. *Atropine* inhibits the cholinergically induced secretion of the stomach and of the pancreas.[84] So atropine was advised in acute pancreatitis.[23] In a retrospective study[11] it was reported to have a beneficial effect on the complication rate in acute pancreatitis. On the other hand atropine must be dosed much higher than possible in humans. This induces tachycardia, mouth dryness, and paralysis of the gut. With lower doses Cameron et al[8] in a controlled study with 51 patients did not find any effect on the course and outcome of acute pancreatitis. The same result was found in an open study.[75] In consequence atropine should no longer be used in the treatment of acute pancreatitis.

1.3. Glucagon, Calcitonin, Somatostatin

These hormones inhibit in pharmacological doses the secretion of enzymes from the pancreas and the secretion of HCl in the stomach. They have been used therefore to set the gland at rest. Favourable effects have been reported for glucagon in acute pancreatitis in a number of uncontrolled series.[54] Carefully controlled studies could not substantiate this impression. Glucagon neither had a beneficial effect on letality[18, 53, 63] nor on the course of the disease.[18, 63, 64, 68] In experimental acute pancreatitis of rats it has no effect.[17, 54] Therefore glucagon can no longer be recommended for treatment of acute pancreatitis. *Synthetic salmon calcitonin* has been investigated in two controlled double blind studies with together 196 patients, mainly with biliary and idiopathic acute pancreatitis and with all grades of severity.[36, 39] Calcitonin lead to a significantly better course of acute pancreatitis in both studies both clinically and biochemically but it did not lower the letality, which was found with and without calcitonin at 9 %. So synthetic salmon calcitonin can be used for stabilisation of the course of the disease. *Somatostatin* inhibits very effectively both the secretion of the stomach and the pancreas. In open studies it was found to have beneficial actions in acute pancreatitis in humans[58, 93] and in dogs.[89] At present a carefully controlled double blind study is carried out in West-Germany but the results are not yet available. So the use of somatostatin in acute pancreatitis is still an experimental therapy. In a case report with use of somatostatin in acute pancreatitis a hyperosmolar coma was observed obviously because of inhibition of insulin secretion.[101]

1.4. Further inhibiting drugs

A number of drugs which inhibit pancreatic secretion has been used in experimental acute pancreatitis:[19] vasopressin, propylthiouracil, isoproterenol, indomethacin, aspirine, prostaglandins. Clinical studies do not exist. Acetazolamide inhibits the production of bicarbonate and fluid in the gland by its action on the carboanhydrase and therefore has been proposed for the treatment of acute pancreatitis.[20] Experimental and controlled clinical studies are not available. Inspissation of pancreatic juice and its actions on acid-base balance are against its use. Glucocorticoids only recently have been discussed with their pros and contras in acute pancreatitis.[21] Induction of acute pancreatitis in severely ill patients and experimentally in animals are heavy arguments against the use of glucocorticoids in this situation.

1.5. Antienzymtherapy with aprotinin, phospholipase-inhibitors and plasminogen-inhibitors

The trypsininhibitor aprotinin (Trasylol[R]) has been widely used in the treatment of acute pancreatitis in the last 15 years. The physiological concept is based on the inhibition of trypsin, kallikrein and kinins which play an important if not decisive role in the pathophysiology of the disease.[40] A large number of favourable reports is found in the literature but all have been uncontrolled with one exception. In 1974 Trapnell et al published a controlled double blind study with aprotinin against placebo in biliary and idiopathic acute pancreatitis with the first attack of the disease and using large doses of the drug.[90] Aprotinin in this study reduced significantly the letality from 25 % in the placebo group to 7 % in the treated group, with significant reduction also in patients over 60 years of age. The positive arguments for aprotinin mainly are based on this study. Before 1974 a number of controlled studies already had not demonstrated an effect of aprotinin.[32] After 1974 three carefully controlled double blind studies have tried to reproduce Trapnell's results, all without a positive finding.[46, 63, 83] Neither the effect on letality nor the beneficial effect on acute pancreatitis in the older patients was reproduced. Some differences between the studies reduce the comparability of the studies. In all three recent studies alcoholic acute pancreatitis was included in which the letality is said to be lower than in the biliary and idiopathic variety.[74] In contrast Imrie et al[46] found a higher letality in the alcoholic form, so this statement is not absolute. In the MRC-study and in Imrie's study the aprotinin was started later than by Trapnell, a possibly decisive difference. Recently the course of the disease with aprotinin in one of the studies has been analysed in detail.[64] There was no difference against the placebo-group. In summary the weight of evidence is very much against the use of aprotinin in the treatment of acute pancreatitis.

Inhibition of phospholipase A_2 by $CaNa_2$-EDTA and procainhydrochloride has been tried in acute pancreatitis,[92] the use being still experimental. The same is true for the application of plasminogen-inhibitors, epsilon-aminocapronicacid and its related compounds. In one clinical study no death was observed in 41 patients against 3 letal cases in the control group,[52] in a further study no beneficial effects were observed.[61]

2. MEASURES TO REMOVE AUTODIGESTIVE ENZYMES AND TOXIC SUBSTANCES

During the process of inflammation exocrine pancreatic enzymes, lysosomal enzymes, toxic products of necrosis, and vasoactive kinins are liberated in large amounts. Two measures have been proposed to remove these substances from the organism: 1. Drainage of the thoracic duct and 2. therapeutical peritoneal lavage. The drainage of the thoracic

duct was used in the sixties but was abandoned again later because of lack of efficacy.[19] *Peritoneal lavage* has been investigated intensively in recent years. Removal of a toxic exsudate from the peritoneal cavity was shown to lower successfully the letality of acute pancreatitis in the rat, the dog and the guinea pig,[55, 56] when the lavage was applied early in the experimental course. Favourable case reports have been published since 1965.[19] Controlled studies were published by Ranson et al,[75, 77] Stone and Fabian[85] and Maroske.[60] Although the letality was not significantly different between the lavage and control groups, an impressive and fast improvement of the 24 hr clinical state of the patients was reported. Stone and Fabian[85] after treatment found amelioration in 29 of 34 patients with peritoneal lavage but only in 13 of 36 patients in the controls without the procedure. Ranson et al[75] had no death during the first 10 days with lavage and 10 deceases in the control group. In conclusion one could say that peritoneal lavage has been proven to be beneficial in the short term and in the severly ill patient. It is not known how it influences the long-term outcome and further controlled studies are needed in this respect.

3. MEASURES TO IMPROVE MICROCIRCULATION

Animal experiments demonstrate that in acute pancreatitis the blood perfusion through the pancreas is diminished.[15] This could help to change the edema into necrosis.[73] Therefore, low molecular dextrans and heparin have been proposed to improve the microcirculation. Low molecular dextrans experimentally increase pancreatic blood flow and oxygen utilisation.[15, 16] Acute experimental pancreatitis in the dog is positively influenced.[99] Goodhead reported on beneficial clinical effects on the course of human pancreatitis.[38] Nevertheless, controlled clinical studies do not exist with dextrans. Arguments for the use of heparin in low doses are an action when consumption coagulopathy is present[22] and an inhibitory action on trypsinogen.[98] Again, clinical studies have not been published. So it can be said that at present the concept of improvement of microcirculation is promising but not clinically proved.

4. SURGICAL ELIMINATION OF NECROSIS BY DRAINAGE OR RESECTION

Early surgical procedures in severe acute pancreatitis have been discussed very controversially in the past years. We will not discuss diagnostic laparotomy, operation because of complications like pseudocysts or abscesses and biliary surgery for stones. Early surgery is done for removal of necrotic toxifying material from the organism.[67] Experimentally dogs survived from acute pancreatitis when total or subtotal pancreatectomy was done early.[67] Positive results with lowering of letality have been reported in uncontrolled series of patients from a number of places.[4, 51, 67] The arguments against surgical procedures of this kind in acute pancreatitis have been put forward by Ranson:[79] 1. Experimentally in a study of Henry and Condon[42] with acute pancreatitis in dogs the total removal of the inflamed pancreas doubled the letality. 2. The replacement of surgical therapy by conservative treatment in the 1930s doubtlessly had lead to a drastic decrease of letality. 3. In all studies which report favourable results of early surgical procedures the letality was compared with older data from the literature or with figures from the surgical departments in severe hemorrhagic pancreatitis before the introduction of early operation, i.e. the data at present available are uncontrolled. 4. Ranson himself in an own prospective controlled study with drainage stopped it after 10 patients because of drastic increase of respiratory and septic complications in the operated patients. 5. Resection often removes not only necrotic but also normal pancreatic tissue which is hidden under the necrosis. This has brought even engaged advocates of early resection to a cautious approach.[10, 96] At present the controversies on early surgery are not yet settled. It seems to be an alternative if under intensive conservative care a steady worsening of the patient's state occurs. Controlled studies on these procedures are urgently needed but are very difficult to plan and to conduct.

5. PROPHYLAXIS AND THERAPY OF COMPLICATIONS

Hypovolemic shock, renal failure, respiratory insufficiency, sepsis are the life-threatening complications[19, 24, 88] which must be recognized and treated as early as possible. Early conservative treatment of these complications mainly has helped to lower the letality of acute pancreatitis in the last decades.[19, 34] Parenteral fluid substitution in prophylaxis of shock is unanimously accepted. Renal dialysis in renal failure and application of oxygen and assisted respiration in the case of drop of arterial pO_2 below 60 mm Hg[45, 65, 70] are well introduced. Controversial are the use of corticosteroids and of antibiotics. Only recently Dreiling et al[21] have discussed *corticosteroids* as being potentially beneficial with an action on shock, on respiratory insufficency, on pancreatic edema and with inhibition of pancreatic secretion. On the other hand it has been shown that steroids do not inhibit stimulated pancreatic secretion in humans.[39] The inhibitions of unstimulated juice leads to an inspissation of the juice which theoretically is perhaps not favourable.[50] It is not established that steroids positively influence hypovolemic shock or respiratory insufficiency. Long-term application of steroids in the rat induces pancreatic damage[6] and clinically many cases have been reported where possibly steroids have induced acute pancreatitis.[19] Controlled studies on the use of steroids in acute pancreatitis do not exist and — based on these arguments — we think that glucocorticoids cannot be recommended at present. *Antibiotics* have been widely used prophylactically in all forms of acute pancreatitis. Nevertheless it is not sure that they are useful in this respect. Pancreatitis primarily is an abacterial inflammation. Secondary infection can occur and lead to abscess formation and sepsis. In four controlled studies a favourable prophylactic effect of ampicillin, cephalotin and lincomycin on the development of bacterial complications was not shown.[12, 27, 44, 85] Together 708 patients with mild and medium severe pancreatitis and with alcoholic etiology were investigated. In the study of Stone and Fabian[85] phlebitis induced by the infusions was doubled in the group with antibiotics. Ampicillin does not penetrate into the pancreatic juice.[80] When sulfamethoxazol and trimethoprim are used the desirable proportion of 20:1 between the two substances is reached neither in pancreatic juice nor in pancreatic tissue.[79a] In conclusion the prophylactic application of antibiotics is no longer justified in alcoholic pancreatitis of mild and medium variety. In the biliary and idiopathic pancreatitis and in severe forms no studies are available. In these cases, therefore, antibiotics should be given for prophylaxis still today.

6. GENERAL SUPPORTIVE MEASURES

The *treatment of pain* sometimes is very urgent in acute pancreatitis. Procainhydrochloride (2 g/day in infusion) has been found to be beneficial and can be applied without side effects.[33, 34] Additional analgetics may be necessary, morphine and its related compounds are forbidden because they increase the pressure of the sphincter muscles. Pethidine may be used in the more severe cases. Aprotinin has been shown conclusively not to act against the pain.[64] Synthetic salmon calcitonin significantly ameliorated pain in two controlled studies.[36, 69]

A special problem which is discussed controversially is *hyperalimentation*. In severe acute pancreatitis the catabolism leads to a rapid weightloss.[25, 27] The pattern of amino acids in muscle tissue and blood points to an increased degradation of muscle.[81] Therefore parenteral hyperalimentation has been proposed.[30] Favourable effects have been reported in some uncontrolled clinical studies, but Goodgame and Fischer could not show this in careful observations.[37] Possibly acute pancreatitis favours the development of complications related to the use of catheters like sepsis.[37] Cerra et al[9] observed that hyperalimentation was unable to counteract autocannibalism as long as the septic process per se was not removed from the organism. So the use of parenteral hyperalimentation is still in the state of an experimental therapy. In patients who had an operation nutrition can be performed by way of a jejunostomy[31, 59] thereby abolishing the risk of a catheter sepsis. Parenteral application of fat emulsions is possible in acute pancreatitis without side effects and without worsering of the pancreatic process.[4, 30, 86]

7. MEASURES TO REMOVE THE CAUSE OF ACUTE PANCREATITIS

Causes of acute pancreatitis which can be removed are biliary disease, alcoholism, primary hyperparathyroidism and certain drugs (i.e. diuretics, steroids, azathioprin etc.). Operative cure of biliary disease in acute pancreatitis is discussed in the surgical literature in detail.[1, 48, 49, 78] A new development is the endoscopic papillotomy for removal of biliary stones in the bile duct during the acute phase of pancreatitis. Acosta et al already had favoured the immediate operation for biliary stones in the first 48 hours, even with sphincterotomy.[1] Safrany et al[82] and Safrany and Cotton[83] introduced the endoscopic papillotomy in 26 patients with acute biliary pancreatitis. In nearly all patients the clinical symptoms were promptly relieved. In no case an unfavourable effect on the autodigestive inflammatory pancreatic process was observed. Recently other groups have reported similar good experiences.[5, 94, 95] Arguments against procedures at the papilla in the acute phase of pancreatitis are derived from surgical experiences.[13, 48, 78] Sphincterotomy itself can induce pancreatitis.[14] At present it is reasonable to concentrate the new method in specialized centres to make possible controlled studies with the best available skill.

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