Clinical and Experimental Artificial Liver Support Today

Gorig BRUNNER

Division of Gastroenterology and Hepatology
University Medical School, Hannover, Germany

Research and development of artificial liver support is laboursome mosaic work. Due to the extreme complexity of the liver progress in artificial liver support is slow. Despite great efforts there is still no breakthrough in artificial liver support.

There would be many indications for the application of true artificial liver support (Table 1). Exact proof of the value or efficacy of an artificial liver support device could best be shown in fulminant hepatic failure as it is assumed that this disease is reversible in the majority of cases if sufficient time can be gained until regeneration has generated sufficient liver cell mass to support the organism. But fulminant hepatic failure is rare making true controlled trials difficult to perform. For truly hopeful new methods multicenter controlled trials or single center trials in large centers have to be performed. Two such trials were performed in the past. The European liver study group performed a controlled trial on the effect of steroids and finally William's group in London performed a controlled trial on charcoal hemoperfusion. While the first study showed a deliterious effect of steroids, the study on charcoal showed no effect.

Although real breakthroughs have not yet occurred, considerable improvements have been made which to a certain extent deserve the term artificial liver support as they support the patient in liver failure or prevent mistakes that have long been made (Table 2).

**IMPROVED INTENSIVE CARE**

Modern analytical techniques guarantee quick and accurate analysis of vital laboratory parameters. This allows rapid correction of disturbances of the homeostasis of the organism with regards to glucose, electrolytes, proteins, clotting factors, etc.

Omitting fructose from liver therapy takes away a hazzard to the diseased liver. Stress ulcer prophylaxis with H2 receptor antagonists has proven to be of significant benefit. The introduction of H2 blockers to the therapy of fulminant hepatic failure has totally eliminated stress ulcer bleeding. Before H2 receptor therapy we have lost almost 20% of our patients in fulminant hepatic failure due to stress ulcer bleedings. These bleedings, preferably from duodenal ulcers, often occurred when the patient had already awakened from coma due to sufficient regeneration at times when one did not expect such complications.

**IMPROVED PLASMA EXCHANGE**

To remove blood or plasma and replace it with fresh blood or fresh frozen plasma has long been an aim in the treatment of fulminant hepatic failure, because theoretically this is an ideal form of artificial liver support. In the early years we organized such treatment by having truck loads of soldiers donate warm blood for our patients and the results were very promising. However such a treatment is not feasible on a large scale. When plasma support became easily available by the use of hollow fiber systems and fresh frozen plasma, a boom in this therapy was noted. However the results were poor. Unforseen problems were encountered and when this treatment was performed too vigorously more people died with this treatment than without. A significant increase in pulmonary cerebral complications were observed resembling acute respiratory distress syndrome and an increase in brain edema was also observed. The reason for this problem was clearly elucidated by Akamatsu and our group.

Aggregates form in stored blood and plasma. These aggregates are caught in the capillary net of the lung where they impair gas exchange and induce pneumonia.

With a simple measure this problem could be overcome. By replacing blood or plasma into the femoral artery and not into a vein lung complications can al-
most be totally prevented. The capillary net of the leg filters the aggregates without side effects to the leg.

**HEMOFILTRATION OR HEMODIALYSIS**

Opolon has shown some time ago that hemodialysis and hemofiltration have a certain detoxifying capacity in liver failure and can prolong survival. But the survival rate could not be improved with this method. However this does not reflect its value as a supportive measure in the treatment of liver failure. Although the majority of toxins appearing in liver failure are lipophilic their precursors, the tremendously increased amino acids as well as the classic toxin ammonia can effectively be removed by dialysis or hemofiltration. A better approach is dialysis with amino acid containing dialysate, as amino acids can be removed without causing an imbalance of the amino acid spectrum. However industry has not taken up this improvement by fabricating amino acid containing concentrates for amino acid dialysis.

**INTRACRANIAL PRESSURE, MONITORING AND TREATMENT**

Although it has long been known, that brain edema is the final cause of death in the majority of patients with fulminant hepatic failure, the only logical consequence was not drawn: Measuring intracranial pressure. Increased intracranial pressure was usually assumed by various clinical signs and findings like convulsions and the judgement of the fundus of the eye. However none of these methods was accurate or in any way scientific. And without accurate diagnosis there is no accurate therapy. With increasing numbers of patients transplanted for fulminant hepatic failure the importance of measuring intracranial pressure soon became evident. After successful transplantation with normally functioning livers several patients would never regain consciousness because they were brain dead or they regained consciousness very delayed demonstrating lasting severe brain damage with spastic paralysis rendering them to stay in curative institutions for the rest of their life.

Continuous measuring of intracranial pressure is now mandatory for every patient with fulminant hepatic failure for immediate detection of increases in intracranial pressure and causative treatment. A bore hole can be safely performed at quick values (thromboplastin time) of 40% and a thrombocyte count of at least 40,000. While the thrombocyte count of 40,000 is seldom a problem, all patients with fulminant hepatic failure by determination have much lower thromboplastin time values. The thromboplastin time values usually lie around 10–15% or lower. Intravascular plasma exchange with 3 liters of fresh frozen plasma is therefore necessary before a pressure transducer can be introduced. After the first plasma exchange the quick values usually lie around 45–55%. We have never seen a complication from boring a hole into the skull when these safety values were observed. We use a Geltic® epidural pressure transducer (Novotronic, Germany). When increases in intracranial pressure are observed, treatment depends on the concomitant findings of the kidney. When kidney function is not impaired, osmotherapy with mannitol is the therapy of choice. When kidney function is impaired, osmotherapy is absolutely contra indicated. In that case a combination therapy with Ranitidine, Theophyllin, Hyperventilation and Hemofiltration becomes necessary. An increase of intracranial pressure of more than 60 mmHg for more than 5–10 min will result in severe damage of the brain from which only very young people can recover. Patients with values over 80 mmHg should not be transplanted. An intracranial pressure higher than the mean arterial pressure results in brain death within minutes. Patients in whom this is observed must never be transplanted.

**SCLEROTHERAPY**

There is no need for sclerotherapy in fulminant hepatic failure. However in patients with liver cirrhosis variceal bleeding can be life threatening by inducing liver failure or maintaining liver failure. Sclerotherapy is now standard therapy not only for stopping acute bleeding but more and more for total eradication as much time can be gained before a transplantation becomes necessary; and in approximately 15% patients never need to be transplanted as therapy of the liver disease after successful sclerotherapy may lead to complete healing as observed in patients with immune hepatitis and other forms of chronic active liver disease. Intervals between sclerotherapy and transplantation in such patients were observed to lie between 6 months and 9 years. In 4 out of 20
patients in liver coma due to bleeding varices the liver disease could be healed after completion of successful sclerotherapy.

**EXPERIMENTAL ARTIFICIAL LIVER SUPPORT**

Many methods have been investigated which did not prove to have true potential application for the future. At the present time experimental research focusses at two major areas.

1. Isolated immobilized and non immobilized hepatocytes for support of liver functions and
2. detoxification with lipophilic hollow-fiber membranes.

**ISOLATED HEPATOCYTES IN MEDIA AND CULTURE IMMOBILIZED AND NON IMMOBILIZED**

The hepatocyte is the smallest unit of the liver exhibiting all liver functions. Therefore it is a good tool for the investigation of liver functions under variable conditions. There are now standard methods for the preparation of hepatocytes from livers which may be modified for different specifications. Standardized methods have also been developed for the storage of isolated hepatocytes. Dimethylsulfoxide (DMSO) and glycerol are the preferred cryoprotectants. Viability after thawing of frozen hepatocytes lies around 60%. Immobilization of hepatocytes preferably in calcium alginate improves their survival and metabolic activity. New sandwich cultures show promising performance. However hepatocytes are still far from clinical application because a number of problems has not yet been solved.

Storage of hepatocytes is still extremely costly and it is almost impossible to store sufficient amounts of hepatocytes to be readily available for clinical use. Data for storage of immobilized hepatocytes do not exist. Hepatocyte cultures are of insufficient quantity to be used. The capacity of all published devices is far from being enough to support liver function in a human scale. The most striking problem is the lack of availability of human cells. Human cells still do not grow in culture. They can be kept alive for many weeks, but they do not proliferate. Artificial liver support devices using hepatocytes however depend on human hepatocytes in order to prevent immune reactions. Therefore as long as the problems of availability of human hepatocytes of sufficient quantity, storage, and stability are not solved, there is no chance for hepatocytes for artificial liver support. Transplantation of hepatocytes into the spleen is a promising technique for chronic liver disease its true value however has yet to be shown.

**LIPOPHILIC HOLLOW FIBER DETOXIFICATION**

Since replacement of total metabolic liver function, as aimed at by the use of hepatocytes is not near, other techniques are under investigation for partial substitution of crucial liver functions. While synthetic products can be replaced by infusion, detoxification is still limited to hydrophilic compounds. Hydrophilic toxins like ammonia can be effectively and safely removed at low cost by hemodialysis. The removal of lipophilic toxins is limited to plasma exchange as all other methods are not safe. But lipophilic toxins are the majority of toxins in liver failure. Therefore an effective and safe method is needed for clinical application. The lipophilic toxins can only be detoxified by direct contact with enzymes or liver cells or they can be removed by the use of the new hollow fiber liquid lipid technology. While enzymes and hepatocytes are not applicable as long as human liver cells and enzymes are not available, at present only the latter method can be applied, whereby all kinds of reactions can be used. With this technique also heterologous hepatocytes and enzymes as well as alkaline solutions can be used, as there is no direct contact of the reactant with the blood of the patient.

With this technique the blood of the patients flows through the lipid hollow fibers. The lipophilic toxins can easily pass the lipophilic hollow fiber membrane. The acceptor solution containing hepatocytes, enzymes, or chemical solutions flows counter stream-wise outside the hollow fiber.

This technique has now been approved for clinical testing. Results are expected in due time.

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