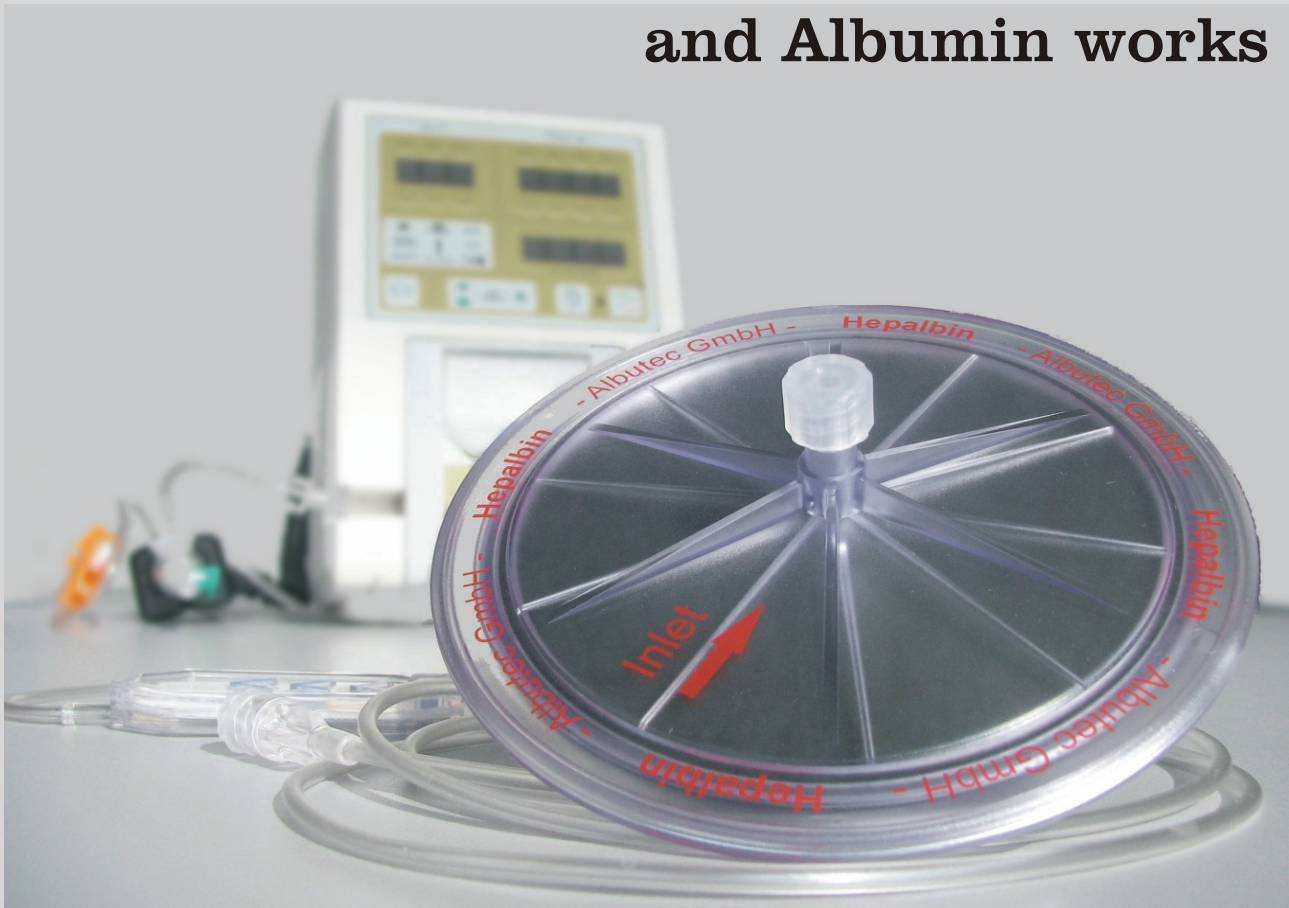


# Hepalbin-Adsorbent

and Albumin works



more safety due to prevention of caprylate and tryptophan accumulation in liver disease patients



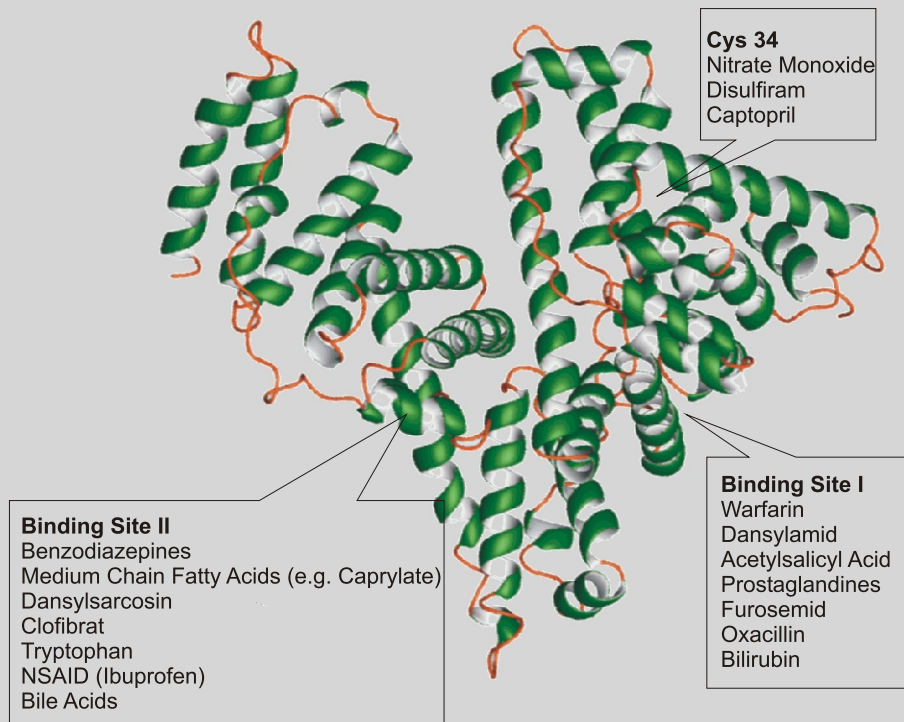
improved therapy by significant enhancement of Albumin Binding Capacity



world wide first technology for bed-side removal of contaminations with caprylate and N-acetyltryptophan

## Human Serum Albumin - a cornerstone of the treatment of severe liver disease

Human Serum Albumin is synthesized in the liver and represents the most important transport molecule in the human organism. In liver failure, the drop of albumin concentration and vasodilation of the splanchnic system are both precipitating severe hemodynamic deterioration. Therefore, albumin is indicated in severe liver failure coupled with hemodynamic deterioration and kidney failure, in order to restore proper perfusion of the kidneys and other critical organs. Recent research data suggest that in addition to providing volume, albumin can also address vasodilation itself provided its binding sites are active. The activity of albumin's binding sites can be measured as the so called Albumin Binding Capacity (ABIC).



## Limits of currently commercially available Human Serum Albumin preparations

Donor derived albumin must be mixed with so called stabilizers during the production process, in order to enable virus inactivation and/or storage over long periods. Usually, the medium chain fatty acid caprylate is used, sometimes combined with N-acetyltryptophan. Both substances bind to the Benzodiazepine Binding Site and induce a conformational change which results in higher thermostability. Both stabilizers can be metabolized by patients with sufficient liver function. However, in severe liver failure, caprylate as well as N-acetyltryptophan accumulate in blood. Since caprylate and tryptophan are well published contributors to complications of liver failure, a precipitation of hepatic encephalopathy and hemodynamic complications are possible.

## Caprylate

Caprylate contributes to the vasodilation and therefore precipitates hemodynamic deterioration. This is caused by inhibition of catecholaminergic activity on smooth muscles, but also by activation of vasoactive prostaglandins. (1)

Caprylate also precipitates hepatic coma and cerebral edema. (2-4)

Current hypothesis suggest that this is mediated by affecting the energy metabolism in the formatio reticularis. (5)

The following effects of caprylate have been demonstrated:

- Inhibition of ammonia reduction by inhibition of urea synthesis. (6, 7)
- Increased oxygen need and ATP consumption of mitochondria due to "decoupling" of oxidative phosphorylation. (8, 9)
- Inhibition of volume control of astrocytes by inhibiting the Na-K-ATPase. (10)
- Enhanced proteolysis in the skeletal muscles combined with inhibition of release of branched chain amino acids, thereby increase of ammonia and decrease of branched chain amino acids in blood. (11, 12, 13, 14).
- Induction of formation of glutamine in the brain by octanoate (caprylate). (15, 16)
- Induction of brain edema by glutamine accumulation in the cells. (17, 18)
- Facilitation of aromatic and indolic amino acid transport into the brain. (20, 21)
- Inhibition of acetylcholin transferase acitivity in the nucleus caudatus. (22)

## N-acetyltryptophan

N-acetyltryptophan is rapidly metabolized to tryptophan. (23-26)

Tryptophan is known to participate in the development of hepatic encephalopathy. (27, 28)

Oxindol, a metabolite of tryptphan is enhanced in liver failure and known to exert neurodepressive acitivities and to induce coma by interacting with neuronal sodium channels. (29-31)

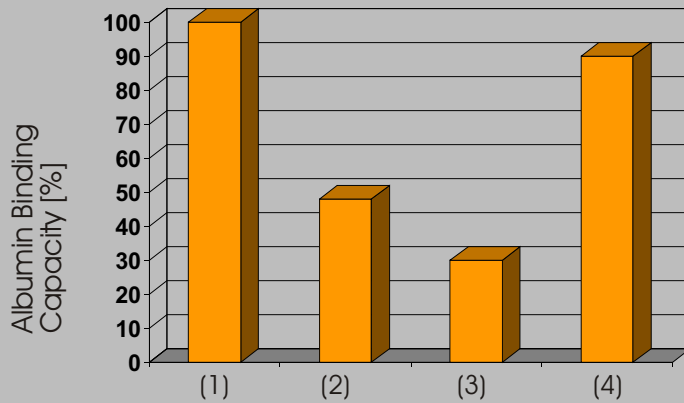
In addition, oxindol can also decrease blood pressure, hence deteriorating hemodynamics.

The unwanted effects of tryptophan are especially enhanced by the fact that in liver failure the amount of unbound tryptophan is specifically increased, most probably due to competitive binding of other toxins, as bile acids, which accumulate in liver failure and displace albumin bound tryptophan. (32, 33)

Specifically the unbound fraction of tryptophan enters the brain. (34)

In the brain, tryptophan interacts with aromatic amino acids and interferes with the metabolism of catecholamines, serotonin and is metabolites (35, 36), which results in a disturbed pattern of neurotransmitters precipitating hepatic encephalopathy and coma. (37-41)

Native albumin does usually not contain caprylate or N-acetyltryptophan. The overwhelming concentration of those substances added in the production process, results into an overloading of the benzodiazepine binding site (Sudlow II). Investigations have shown that the Albumin Binding Capacity of commercial albumin solutions is reduced by those substances to 30-40%. An improvement of patients Albumin Binding Capacity by using commercial albumin is therefore not possible. Actually there is a risk that caprylate and tryptophan can displace toxic metabolites from patient's albumin once they enter the circulation (42, 43) which would result into a higher toxicity due to higher bioavailability (44).



#### Binding behavior in different albumin samples

- (1) physiologic
- (2) liver failure
- (3) commercial albumin preparations
- (4) Hepalbin treated

#### Solution/Results

Albutec GmbH offers a new CE certified medical device, the Hepalbin-Adsorbent, which enables the bed-side removal of unwanted contaminations with caprylate and N-acetyltryptophan and provides thereby a product, which resolves the conflict between the need for stabilizers during production and storage and the desire for clean albumin with available binding sites after infusion into liver disease patients. Until recently, a removal of caprylate appeared impossible, as it is extremely tightly bound to albumin.

Measurements of caprylate and N-acetyltryptophan concentrations in commercial albumin preparations before and after passage of the Hepalbin-Adsorbent have proven that the initial concentration of caprylate (1600  $\mu\text{mol}$  in 100 ml 20% albumin) could be reduced to only 8.7  $\mu\text{mol}$  and the ratio of caprylate to albumin could be reduced from 5.3 to 0.029. Starting from similar concentrations, N-acetyltryptophan was reduced below the detection limit (<10  $\mu\text{mol}$ ) and the ratio between N-acetyltryptophan/albumin (mol/mol) could be reduced from 5,3 to less than 0,033.

Measurements of the binding activities have shown that the severe stabilizer-associated reduction seen in commercial albumin solutions could be completely reversed after passage of the Hepalbin-Adsorbent and reached normal levels (>95%). Therefore, infusion of 1 g Hepalbin-Adsorbent processed albumin exerts a comparable binding activity of 3 g or more of commercial albumin solutions.

Considering the well published severe risks associated with caprylate and N-acetyltryptophan for patients with severe liver failure and the good biocompatibility of the product, the Hepalbin-Adsorbent represents a significant progress in the treatment of liver failure patients.



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