







Hepalbin[®]-Adsorbent

And Albumin works - even better!



-  Unique Technology for Bed-Side Optimization of Human Albumin World Wide
-  More Effective Therapy by Improvement of Albumin Binding Capacity
-  Reduction of Adverse Events caused by Caprylate and Tryptophanate in Albumin Solutions applied to Patients with Liver Disease
-  **First Clinical Studies confirm improved Efficacy of Albumin on Renal Function, Hemodynamics and Cerebral Function**
-  **LESS is MORE - Extended Use in Albumin Dialysis**

Human Albumin

The standard of care in the treatment of complications of portal hypertension in liver cirrhosis includes the infusion of Albumin. Specifically the therapy of refractory ascites, spontaneous bacterial peritonitis and hepatorenal syndrome require the use of Albumin as a plasma expander, which is supported by prospective controlled trials. The advantage of Albumin in comparison to synthetic plasma expanders (e.g. starch) has been associated with additional biological functions, as the ability to bind smaller molecules of pathophysiological relevance.

Unfortunately, commercial Albumin must undergo the process of virus inactivation and storage (up to 5 years), both requiring the industrial addition of caprylate and frequently additional acetyltryptophanate. Both substances bind to the benzodiazepine site of Albumin and significantly reduce commercial Albumins Binding Capacity (ABiC) for ligands, e.g. toxins.

The ability to bind toxins relevant in liver failure can be measured by testing the ABiC for markers. Clinical studies have shown that the ABiC of patients Albumin in liver failure is significantly reduced which correlates to the degree of liver disease (MELD and CTP) [REF 1]. This Observation has been explained by the occupation of Albumin by toxins, which accumulate in liver failure. Pharmaceutical Albumin preparations are characterized by an extremely reduced ABiC, a consequence of the (more than 5-10-fold per molecule) overload with caprylate and acetyltryptophanate. If infused in patients with liver failure, those substances not only reduce the therapeutic effect of Albumin by occupying the needed binding sites, but have also been shown to have undesired adverse events on hepatic encephalopathy, hemodynamic stability and renal function. As the liver plays an important role in the metabolism of caprylate and acetyltryptophanate, the risk to accumulate toxic levels by Albumin infusion is even higher in liver disease. Regulatory authorities (e.g. FDA) have published the potential adverse events of caprylate:

Biological Effects

FDA about caprylate effects [Ref. 2]:

1. hypoglycemia
2. hyperventilation
3. **narcotic action*** in various animal species
4. increased oxygen consumption and decreased clearance of long-chain fatty acids by the liver
5. **vasodilation***
6. **decreased muscle contractility***
7. **altered*** epithelial and membrane **permeability***, including alteration of **the blood-brain barrier***
8. inhibition of platelet reactivity
9. increased release of insulin and enzymes from pancreatic cells
10. altered carbohydrate metabolism, including glucose production
11. increased catabolism of muscle proteins, decreased incorporation of amino acids into protein and alterations in amino acid metabolism
12. **decreased ammonia*** production and **metabolism***
13. depressed synthesis of DNA (Deoxyribonucleic acid) and RNA (ribonucleic acid)

* those effects precipitate complications of liver failure: hepatic encephalopathy, hypotension and renal failure



Solution

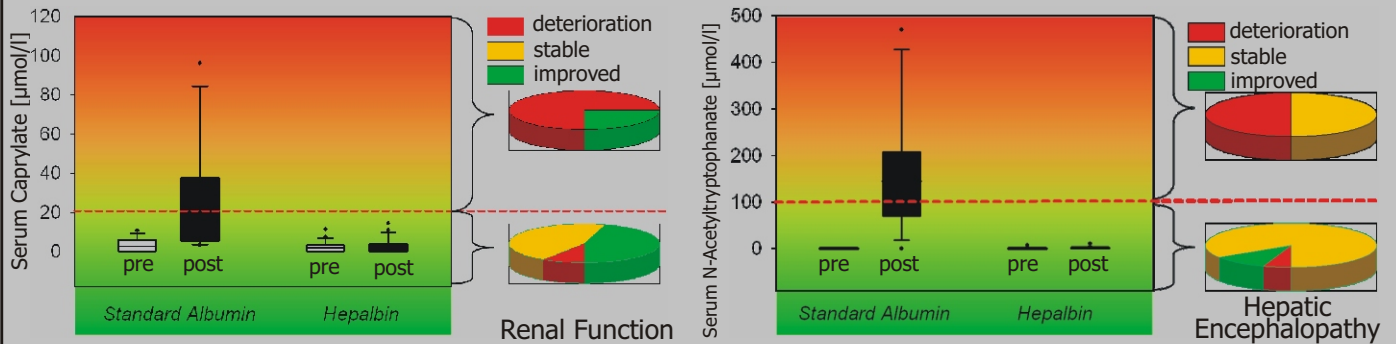


Albutec GmbH offers a CE-certified medical device component for the infusion lines, which allows the bed-side elimination of caprylate and acetyltryptophanate. Thus, once passed through the Hepalbin-Adsorbent, the Albumin has regained its unique binding activity as it is detectable in healthy donors. Therefore, by reduction of adverse events and by normalizing Albumins binding capacity, the therapeutic efficacy of Albumin in complications of liver disease has improved, as shown by clinical research.

Results of Clinical Studies

In order to identify the actual clinical consequences of caprylate and acetyltryptophanate in Albumin solutions applied in liver failure, a clinical protocol has been applied to compare the effect of Albumin infusion with and without caprylate and acetyltryptophanate in refractory ascites, spontaneous bacterial peritonitis and hepatorenal syndrome.

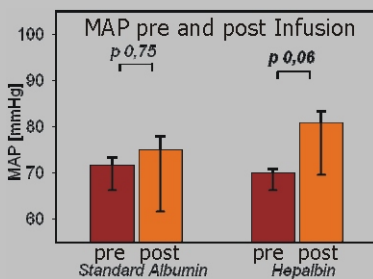
Renal and Cerebral Function stabilized in Hepalbin Group



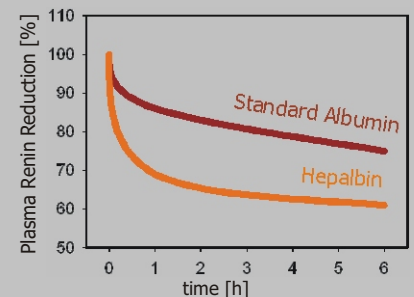
The disturbed metabolism of caprylate and acetyltryptophanate in liver failure resulted in a significant accumulation of both substances in the control group. Serum caprylate levels higher than 21 µmol/l were associated with a high incidence of affected renal function (in 75% of patients) as presented by increasing creatinine. Serum acetyltryptophanate levels higher than 100 µmol/l were associated with a higher incidence of deterioration of hepatic encephalopathy (50% of patients).

In none of the patients, who received the Albumin via the Hepalbin-Adsorbent, an accumulation of caprylate or acetyltryptophanate was observed, which was associated with even better albumin efficacy. In 45% of the patients an improvement of renal function was seen and in additional 45% the creatinine level remained stable. In parallel, the cerebral function did not deteriorate in more than 90%.

Albumin Efficacy on Hemodynamics improved in Hepalbin Group

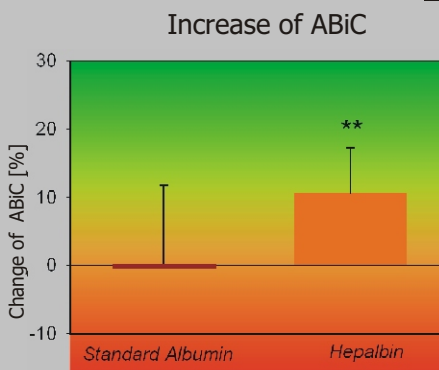


Renal and cerebral functions are affected by hemodynamics. As caprylate and acetyltryptophanate have been shown to induce vasodilation, plasma renin as a marker for the effective blood volume and the mean arterial pressure (MAP) was recorded.



The infusion of caprylate and acetyltryptophanate free Albumin resulted in a more significant improvement of pathological plasma renin levels and an improvement of mean arterial pressure in severe hypotensive patients (MAP < 75 mmHg).

Albumin Binding Capacity improved in Hepalbin Group



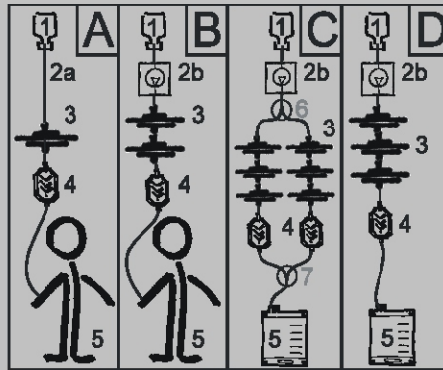
Clinical studies have shown that the Albumin Binding Capacity (ABiC) as a parameter for the affinity of the benzodiazepine binding site of patients Albumin is a prognostic parameter, which not only correlates with prognostic scores like MELD and CTP, but also indicates an improved outcome when normalized during interventional therapies as Albumin dialysis.

An improvement of ABiC above 50% reduces mortality [Ref. 3]. As caprylate and acetyltryptophanate occupy the benzodiazepine binding site of pharmaceutical Albumin, ABiC remained unaffected by standard Albumin infusion, whereas the infusion of Albumin via the Hepalbin-Adsorbent increased the patients ABiC significantly up to 24 hours, which could also explain the favourable clinical effects on hemodynamic, renal and cerebral function.

Intended Use of Hepalbin®-Adsorbent

Application of Hepalbin-Adsorbent for i.v. use and for Albumin Dialysis:

- Application of a single Hepalbin-Adsorbent to process 100 ml can be done without an infusion pump
- Removal of stabilizers from Human Albumin solutions of more than 100 ml for i.v. use, e.g. after paracentesis, now possible by combination of adsorbents
- For preparation of very large Albumin pools for Albumin Dialysis, e.g. applying SPAD or MARS (Molecular Adsorbents Recirculating System), specific procedures have been developed



Examples

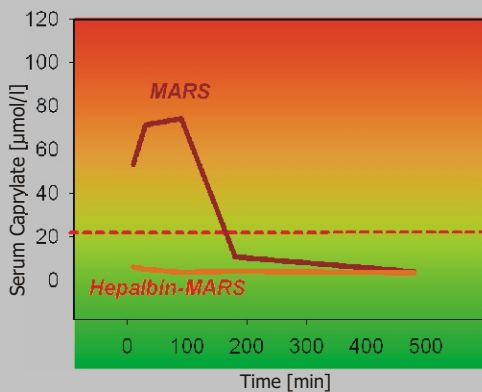
- A:** Infusion of 100 ml Human Albumin with infusion pump or by gravity possible;
- B:** Infusion of 200 ml Human Albumin;
- C:** Preparation of 700 or 800 ml Human Albumin for preparing Albumin dialysis solutions for SPAD;
- D:** Preparation of 300-400 ml Albumin for MARS.

Legend:

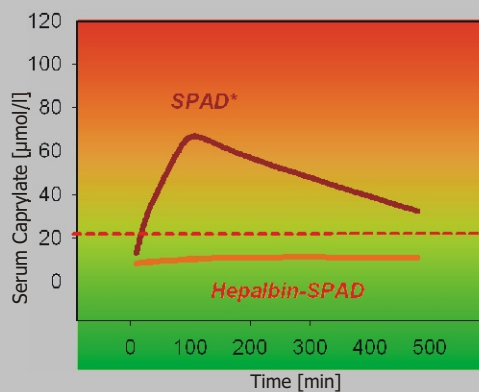
- 1 Human Albumin solution 20%
- 2 Infusion System 2a without, 2b with Infusion pump
- 3 Hepalbin-Adsorbent
- 4 Particle Filter
- 5 A, B venous patient access; C, D collection bag
- 6 "Y"-Adapter
- 7 3-Way Stop Cock

Albumin Dialysis & Hepalbin®-Adsorbent

Elimination of Undesireable Adverse Events on Renal and Cerebral Function



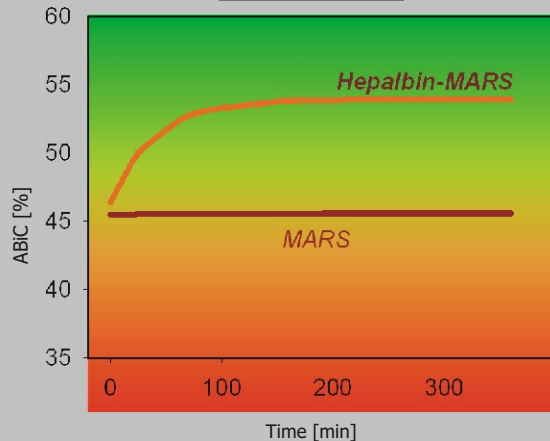
Adverse Events on Kidney Function possible



Adverse Events on Kidney Function possible

*SPAD: Single Pass Albumin Dialysis

Improvement of prognostic Parameters



- Every Extracorporeal Albumin Dialysis Therapy (ECAD) using pharmaceutical Albumin results in an introduction of caprylate (and frequently acetyltryptophanate) to the patient.
- In addition to well documented adverse events, caprylate and acetyltryptophanate compromise the benefits of Albumin Dialysis on renal and cerebral function and therefore compromise the risk/cost/benefit ratio of Albumin Dialysis.
- The Hepalbin-Adsorbent can eliminate the risk of caprylate and acetyltryptophanate accumulation during Albumin Dialysis.
- In a standardized model, Albumin Dialysis using Albumin, which was processed by the Hepalbin-Adsorbent, had a significantly higher effect on the prognostic parameter ABiC than Albumin Dialysis using normal Albumin.

References:

- Ref. 1:** Klammt S. et al.: Albumin-binding function is reduced in patients with decompensated cirrhosis and correlates inversely with severity of liver disease assessed by model for end-stage liver disease; Eur J Gastroenterol Hepatol; 2007 Mar. 19 (3):257-63
- Ref. 2:** Department of Health and Human Services/Food and Drug Administration, 21 CFR Part 640 [Docket No. 98N-0608], published in Federal Register/Vol. 65, No. 167, August 28, 2000, page 52017
- Ref. 3:** Klammt S. et al.: Improvement of impaired Albumin Binding Capacity in Acute on Chronic Liver Failure by Albumin Dialysis. Liver Transplantation 2008, in press



LBUTE GmbH

Fon: +49-381-12165871
Fax: +49-381-12165877

Albutec GmbH
Schillingallee 68
18057 Rostock
Germany

www.albutec.de
info@albutec.de

