

# COMMERCIAL ALBUMIN CONTAINING CAPRYLATE (=OCTANOATE) AS CONSERVATIVE MAY BE LIMITED TO EXERT ITS CLINICAL EFFECT AS PLASMA EXPANDER IN LIVER FAILURE WITH RENAL DYSFUNCTION

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## Background

When albumin was established as a blood substitute in World War II, there was an urgent need for stabilizing agents to ensure the proteins stability which was realized by adding octanoic acid (caprylate) and N-acetyltryptophan (NAT) which both can be metabolised in healthy humans. It was only many years later, that basic science research discovered, that caprylate and NAT or its metabolites are involved in the pathogenesis of hepatic coma, vasodilatation and hypotension and renal failure. Controlled trials investigating the effect of albumin in complications of liver cirrhosis have shown, that albumin can improve clinically meaningful endpoints in complications of portal hypertension. However the risk of caprylate and NAT accumulating due to organ failure and causing unwanted effects potentially limiting or even counteracting the effects of albumin remained unknown, as no albumin free of said contaminants was available as a control.

## Patients and Methods

### Study Design and Inclusion/Exclusion Criteria

In order to differentiate the effect of albumin from potential adverse events of caprylate and NAT, two groups of patients were treated prospectively. One group received albumin with commercial albumin containing said substances and one group received the albumin via a nanostructured charcoal filter designed to reduce the content of caprylate and NAT by more than 95%.

Patients *included* in the study had cirrhosis and complications presenting indications for albumin infusion based on the following conditions:

- refractory ascites with need for paracentesis
- spontaneous bacterial peritonitis
- hepatorenal syndrome

Patients were *excluded* from the study when presenting one of the following conditions:

- Active bleeding
- Indications for fresh frozen plasma infusion within the next 24 hours

17 patients received standard commercial albumin unfiltered and 25 patients received filtered albumin.

### Endpoints

In order to observe the in vivo kinetic, plasma caprylate and NAT were measured before and after infusion by headspace gas chromatography or HPLC respectively. As clinical parameters, hepatic encephalopathy and plasma creatinine were evaluated within 24 hours. All patients underwent blood pressure monitoring.

Data are presented as medians (min-max), changes in concentrations were compared by nonparametric tests for paired samples, comparisons between groups by MWU-test.

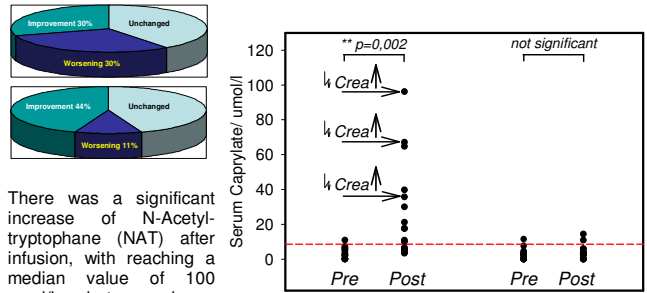
## Results

40 Patients were enrolled between August 2007 and May 2008, with 25 Patients receiving filtered albumin (Caprylate and NAT depleted) and 15 Patients receiving standard albumin. The Baseline characteristics were comparable between the groups and are listed in table 1.

Table 1

Baseline Parameters (all non significant)	Standard Albumin Group; n=15	Filtered Albumin Group; n=25
Age	63(46-77)	60,5 (45-83)
Sex	11 Males 4 Females	18 Males 7 Females
Albumin Administration	200 (100-600)	200 (100-500)
Creatinine (umol/l)	109 (75-393)	130 (75-647)
Total Bilirubin(mg/dl)	3.04 (1.27-14.4)	2.86 (0.36-31.75)
Albumin (3.5-5.0 g/dL)	2.47 (2.09-4.05)	2.74 (1.87-3.86)
INR <sub>v</sub>	1.26 (1.08-2.15)	1.49 (1.08-2.09)
<b>Primary Liver Disease</b>		
Alcoholic Liver Disease	12	22
Other	3	3
<b>i.v. Albumin indicated for</b>		
Paracentesis	11	17
Hepatorenal Syndrome	4	7
SBP	0	1
CTP Score	10 (7-12)	10 (7-13)
MELD Score	19.9 (8-36)	18.8 (12-40)

Figure 1 and 2: Course of Creatinine in 24 hours and Caprylate



There was a significant increase of N-Acetyltryptophane (NAT) after infusion, with reaching a median value of 100 umol/l, but maximum levels of 470 umol/l.

NAT is not a physiological component in humans, but is metabolized to tryptophane. Although the half life time of caprylate in healthy individuals (35 seconds) would not allow a measurable increase of caprylate, there was a significant increase of caprylate after infusion in the group of cirrhotic patients that received standard albumin, which could be prevented by bed-side filtration (see figure).

Of note, the standard serum level of caprylate should be below 6 umol/l, as it usually does not play a physiological role as a fatty acid in humans.

The 24 hour creatinine course indicated a significant increase (worsening) only in 11% of the patients of the group receiving filtered albumin, but approximately in a third (30%) of the group receiving standard albumin.

Most concerning was that all patients presenting a worsening of creatinine within 24 hours, where also among those with very sharp increases of caprylate.

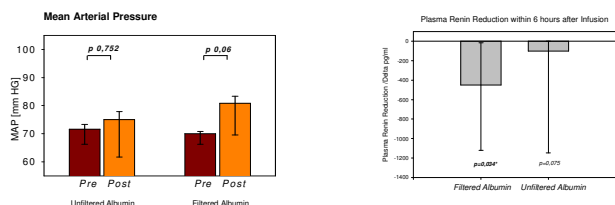
Patients in the filtered group also had an improvement of urine output whereas the standard group did not.

Biochemically, the difference between the groups in the course of plasma caprylate and NAT was also associated with a significant (p<0.01) improvement of patients albumin binding capacity for the benzodiazepine binding site marker Dansylsarkosine (ABIC) by 10% only in the group receiving filtered albumin, a binding site, that is also capable to bind vasoactive metabolites which can cause vasodilatation.

This was also associated with a stronger tendency for mean arterial pressure (MAP) improvement and renin reduction.

There were also 30% in the group receiving standard albumin with worsening of HE versus 8% in the filtered group. In the filtered group, HE improved in 16% whereas no improvement was seen in the standard group. However, in both groups HE remained unchanged in approximately two third of the patients.

Figure 3 and 4: Hemodynamics



## Conclusion

In conclusion, controlled investigation has shown, that in patients with liver dysfunction, caprylate and N-Acetyltryptophane -are accumulating when given with albumin -are indeed associated with signs of vasodilatation -may affect albumins capability to restore renal perfusion and function.

As this indicates potential adverse effects of the classical stabilizers in liver dysfunction, this should be followed by larger studies.