

CAPRYLATE REDUCED ALBUMIN DIALYSIS REDUCES RISK OF OXIDATIVE TUBULAR INJURY IN RENAL FAILURE SECONDARY TO LIVER FAILURE

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Background:

Single pass albumin dialysis (SPAD) has been suggested as a simplified method of MARS which is capable of removing albumin bound toxins and supporting the liver (Sauer et al. Hepatology 2004).

Problem:

Plasma industry adds caprylate (octanoate) and acetyltryptophanate (Ac-Try) to commercial albumin solutions as stabilizers.

Caprylate and acetyltryptophanate are harmless if metabolized by a healthy liver.

HOWEVER, in liver disease, both stabilizers or its metabolites accumulate and participate in the induction of:

- HEPATIC COMA
- VASODILATION, HYPOTENSION AND SHOCK
- OXIDATIVE RENAL INJURY

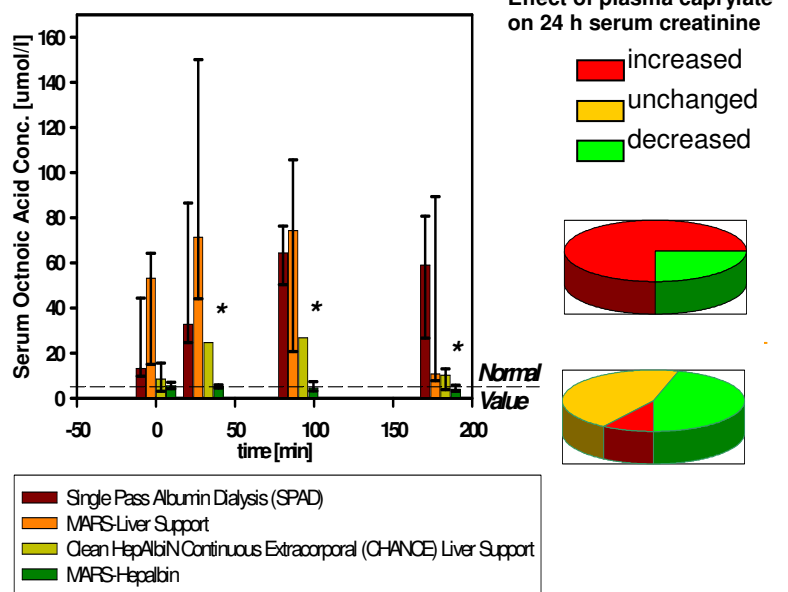
Single pass albumin dialysis (SPAD) exposes liver failure patients to 18 l of a 4 mmolar Ac-Try and 4 mmolar caprylate solution within 12 hours. MARS exposes patients to 600 ml of 16 mmolar caprylate and Ac-Try.

Aim:

To investigate the transfer of caprylate in SPAD and MARS into blood with normal and caprylate/Ac-Try free albumin.

Results:

Middle Chain Fatty Acids in various Liver Support Therapies



Conclusion:

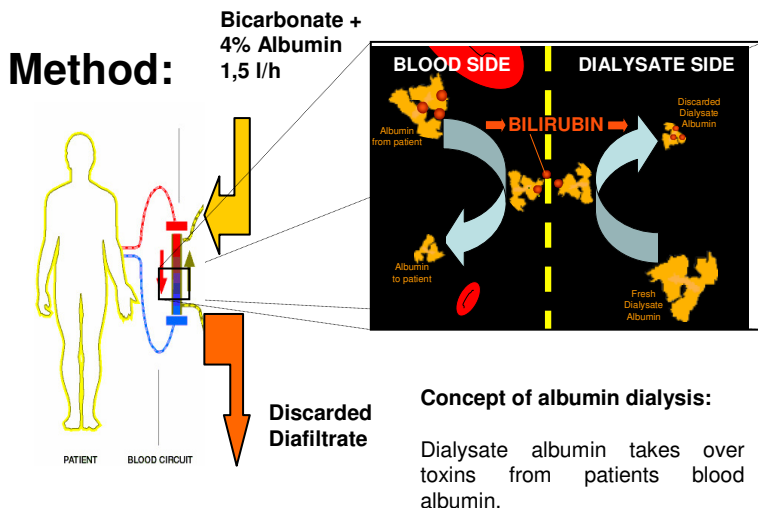
Single pass albumin dialysis (SPAD) does induce accumulation of caprylate in patients blood.

In 12 h SPAD, patients are exposed to 72 mmol caprylate and Ac-Try, whereas in MARS only to 9,6 mmol, due to the limited amount of albumin.

Clinical implications NEED to be investigated in a controlled study with CLINICAL endpoints.

Albumin, free of toxic stabilizers is desired for ANY therapy applied to patients with liver failure.

Method:



We performed with standard albumin 6 consecutive SPAD treatments in 2 patients and 6 MARS treatments in 2 patients.

We also used caprylate/Ac-Try free albumin (Hepalbin Albutec GmbH Rostock) in 6 single pass sessions (CHANCE) and in 5 MARS sessions.

Samples were taken at the beginning and after 30, 90, 180 and 480 minutes in the blood inflow to the dialyzer and from the blood outflow of the dialyzer. Also, samples were taken from the dialysate in- and outflow.

Plasma caprylate was detected by Headspace Gas Chromatography and Mass Spectrometry.

Values are displayed as means (SD).

References

- Kragh-Hansen, U. "Octanoate binding to the indole- and benzodiazepine-binding region of human serum albumin". *Biochem. J.* 270 (1991): 641-644.
- Nicotri, T.A.G., Weiner, I.W., Hage, D.S. "Allosteric and competitive displacement of drugs from human serum albumin by octanoic acid, as revealed by high-performance liquid affinity chromatography, on a human serum albumin-based stationary phase". *J. Chromatogr.* 577 (1992): 305-315.
- Kistev, A., Mikov, D., Lukarova, J. "Effects of the medium chain octanoic fatty acid on the contractile activity of vascular smooth muscle tissues". *Folia Medica (Plovdiv)* 1 (1992): 12-18.
- Mullen, K.D., Sarbah, S.A., Kyriakou, A. "Perioperative encephalopathy". *Liver Disease. Diagnosis and management.* Hg. B.R. Bacon and A.M. DiBeseigne. New York: Churchill Livingstone, 2000. 251-260.
- Zieve, L. "Role of synergism in the pathogenesis of hepatic encephalopathy". *Hepatic encephalopathy in chronic liver failure.* New York: Plenum Publishing Corp., 1984. 15-23.
- McCandless D.W. "Octanoic acid-induced coma and reticular formation energy metabolism". *Brain Res.* 335 (1985): 131-137.
- Mikov, D. "Influence of fatty acids on the detoxification of ammonium in the liver: implications for hepatic encephalopathy". *Advances in Neurology/Metabolism and Hepatic Encephalopathy.* Hg. P.B. Scuderi. Amsterdam: Elsevier, 1998. 103-110.
- Zieve, L., Derr, R.F. "Methanethiol and fatty acids depress urea synthesis by the isolated perfused rat liver". *Gastroenterology* 80 (1981): 1320.
- Parker, W.D., Jr., Haas, R., Stumpf, D.A., Eguren, L.A. "Effects of octanoate on rat brain and liver mitochondria". *Neurology* 33 (1983): 1374-1377.
- Wojcicka, L., Schrieffel, P. "Effect of fatty acids on energy coupling processes in mitochondria". *Biochim. Biophys. Acta* 1183 (1993): 41-57.
- Kristov, A., Mikov, D., Lukarova, J. "Effects of the medium chain octanoic fatty acid on the contractile activity of vascular smooth muscle tissues". *Folia Medica (Plovdiv)* 1 (1992): 12-18.
- Cleary, J.E., Holtzman, D., Sankar, R., Lawson, C., Rosenberger, R. "Octanoic acid inhibits astrocyte volume control: implications for cerebral edema in Reye's syndrome". *J. Neurochem.* 52 (1989): 1197-1202.
- Curzon, G., Knott, P.J. "Environmental, toxicological and related aspects of tryptophan metabolism with particular reference to the central nervous system". *CRC Crit. Rev. Toxicol.* 5 (1977): 145-167.
- Mikov, D. "The role of the octanoic fatty acid in the pathogenesis of the metabolic alkalosis in experimental liver failure". *Folia Medica (Plovdiv)* 35 (1993): 29-37.
- Elli, A.T., Oatason, S., Thermen, G., Butlerworth, R.F. "Ammonia-induced brain edema and intracranial hypertension in rats after portal-caval anastomosis". *Hepatology* 19 (1994): 1437-1444.
- Norenberg, M.D., Bendier, A.S. "Astrocyte swelling in liver failure: role of glutamine and benzodiazepines". *Acta Neurochir. Suppl.* 60 (1984): 24-27.
- James, J.H., Zeparo, V., Jeppsson, B., Fischer, J.E. "Hyperammonemia, plasma amino acid imbalance, and blood-brain amino acid transport: a unified theory of portal systemic encephalopathy". *Lancet* 2 (1979): 772-775.
- Shore, R., Caradell-Caragano, P., Fiori, A., Coci, F., Rossi Fanelli, F., Cangiano, C. "Ammonia, methylmercaptan, and blood-brain transport of amino acids". *Advances in hepatic encephalopathy and urea cycle diseases.* Basel: Karger, 1984. 273-289.
- Ono, J., Hudson, D.G., Domingo, R.S., Lew, J.L., Livingston, A., Zeppa, R. "Tryptophan and hepatic coma". *Gastroenterology* 74 (1978): 196-200.
- Knott, A.J., Davidson, A.R., Williams, R., Kastanmanem, B.D., Curzon, G. "Dopamine and serotonin metabolism in hepatic encephalopathy". *Brit. Med. J.* 1 (1974): 549-551.
- Carpenedo, R., Marinoni, G., Moroni, F. "Oxindole, a sedative tryptophan metabolite, accumulates in blood and brain of rats with acute hepatic failure". *Neurochem. J.* 19 (1986): 1999-2003.
- Mannioni, G., Carpenedo, R., Corradetti, R., Carla, V., Venturini, L., Baraldi, M., Zenzeri, M., Moroni, F. "Tryptophan metabolism and hepatic encephalopathy: Studies on the sedative properties of oxindole". *Adv. Exp. Med. Biol.* 467 (1999): 155-167.
- Moroni, F., Carpenedo, R., Venturini, L., Baraldi, M., Zenzeri, M.L. "Oxindole in the pathogenesis of hepatic encephalopathy". *Lancet* 351 (1998): 1861.
- Al Martini, H., Hamman, E.J., Insa, P.G., Bartlett, K., Record, C.O. "Brain indoles in human hepatic encephalopathy". *Hepatology* 17 (1993): 1033-1040.
- Borg, J., Warner, J.M., Schlienger, J.L., Inbar, M., Manescau, C., Maq, G. "Neurotransmitter modifications in human cerebrospinal fluid and serum during hepatic encephalopathy". *J. Neurol. Sci.* 57 (1982): 343-356.
- Bergstrom, M., Reader, T.A., Butlerworth, R.F. "Early changes of serotonin turnover in brain following portal-caval anastomosis: relation to altered sleep patterns and diurnal rhythms?". *Progress in Hepatic Encephalopathy and Metabolic Nitrogen Exchange.* Hg. F. Bengtsson. Boca Raton: CRC Press, 1991. 219-232.
- Fennstrom, J.D., Wurman, R.J. "Brain serotonin content: Physiological regulation by plasma neutral amino acids". *Science* 178 (1972): 414-416.
- Hansen, M., Bourquin, S., Morel-Gaudry, Y., Hery, F., Glowinski, J. "Role of active transport of tryptophan in the control of 5-hydroxytryptamine biosynthesis". *Adv. Biochem. Psychopharmacol.* 11 (1974): 153-162.
- Hartmann, E., Spreitzer, C.L. "Sleep induced by L-tryptophan". *Nouv. Rev. Med.* 167 (1979): 497-499.
- Hörtnagl, H., Lochs, H., Körbinger, G., Hackl, J.M., Harmele, A.F., Binder, H., Wiewerska, F. "Plasma catecholamines in hepatic coma and liver cirrhosis: Role of octopamine". *Klin. Wochschr.* 59 (1981): 1159-1164.