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Long-term effectiveness of high-dosed ornithine-aspartate on urea synthesis rate and portal hypertension in human liver cirrhosis

D. Müting, J.-F. Kalk, and **Chr.-P. Klein**

Heinz-Kalk-Krankenhaus, Bad Kissingen, Federal Republic of Germany

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Summary. The effectiveness of ammonia reducing amino acids on hyperammonemia and hepatic encephalopathy is well known in patients suffering from liver cirrhosis. Data concerning long-term therapy on hepatic function and urea synthesis rate (UNSR) are still lacking. According to Vilstrup/Poulsen it is a good standard for functioning liver mass. Therefore, 25 patients with histologically proven liver cirrhosis and distinct portal hypertension were treated daily with 9 gr. ornithinasparte over 13 years (8–20 years). Shunt operations, esophageal varicosis sclerosis, or portal pressure reducing medication were not applied. Rigorous alcohol abstinence and 60 gr protein/day were prescribed. During the investigation, 3 laparoscopies and 4 liver biopsies were performed, on the average, on each individual. Significant improvements of clinical and biochemical results (Child-Pugh-Index; Composite Clinical and Laboratory Index) were obtained during the long-term therapy with ornithine-aspartate. Esophageal varicosis II-III was either reduced to 0-I or totally eliminated. Also significant was an increased urea synthesis rate and a decreased hyperammonemia.

A plausible explanation for the long-term therapy effectiveness with ornithine-aspartate is the possible recovery of the functioning mass without hepatic size increase. Also important is the rigorous alcohol abstinence. It leads to a significant reduction of portal hypertension in patients suffering from alcohol induced liver cirrhosis (Reynolds, own observations).

Additional favorable factors are intensive muscle training and absence of gastrointestinal bleeds.

Keywords: Amino acids – Liver cirrhosis – Ornithine-aspartate – Long-term treatment – Urea synthesis rate

Introduction

The effectiveness of ammonia reducing amino acids on hyperammonemia and hepatic encephalopathy is well known in patients suffering from liver cirrhosis. But data concerning the effect of a long-term therapy on hepatic function and urea synthesis rate (UNSR) are still lacking. According to Vilstrup UNSR is a good standard for the functioning liver mass.

Methods

Urea synthesis rate (UNSR)

Imperative for the determination of the UNSR are quantitative collections of 24-hour urine, and standardized metabolic conditions for the patient. The quantitative collection of the 24-hour urine must be controlled by determining its creatinine content. To avoid a fermentative formation of urea in the standing urine, it must in every case be mixed with thymol at onset. A simultaneous determination of urea-N in the serum of pre-prandial blood (BUN, Blood Urea Nitrogen) is necessary on the first, and third day. The quantitative determination of urea in serum, and in 24-hour urine is then carried out with the colorimetric urease method from Boehringer Mannheim. Quantitative determinations for plasma ammonia and other biochemical methods see Müting, 1988.

The UNSR is finally calculated according to the following formula.

$$\frac{PU = UUN \times 2.14 \times \text{volume} + (BUN_2 - BUN_1 \times 0.06 \times kg \times F}{2.8}$$

PU = production of urea (g urea/24 h); UUN = urea nitrogen in urine (g/l); Vol. = volumen of the 24 h urine; BUN_1 = blood urea nitrogen at the beginning of the 24 h urine collection (mg/100 ml); BUN_2 = blood urea nitrogen at the end of the 24 h urine collection; kg = body weight (kg); F = factor for the calculation of body fluid, =0.55 female, 0.60 male; 2.8 = factor: conversion from mg/dl into mmol/l.

Material

Alcoholic cirrhosis in 9 cases, virus B-induced hepatitic cirrhosis in 11, and haemochromatosis in 5 patients (18 men and 7 women). The average age of the patients was 58 +/− 13 years (range: 38–88), mean height 172 cm and mean weight 71.5 kg. In all 25 patients, the diagnosis had been confirmed by laparoscopy and liver histology; during the course of the condition, an average of 2 to 4 laparoscopies with guided liver biopsies, as well as 3 to 5 percutaneous biopsies were performed for monitoring purposes. All endoscopic evaluations of the oesophageal varices were performed serially at stationary admittance, before dismissal, and subsequently ambulatory using the newest Olympus fiber optic endoscope of the time. All 25 patients were submitted to at least 10–30 endoscopic controls of their oesophageal varices during the course of 13 years. The average observation period was 13 years (range: 8–20 yr). Within this period, 3 patients died at home. No death was caused by gastrointestinal bleeding. One was due to sigmoid carcinoma with metastatic liver, another due to hepatocellular carcinoma, and the third due to pneumonia. Their initial oesophageal varices regressed rapidly from individually II-III to I-II during the state of strict abstinence from alcohol, and remained unchanged after alcohol uptake was resumed. Of the 6 patients with ascites at onset, four had only a salt restriction diet, one had saluretics, and one had spironolactone for 3 months. Portal pressure is certainly reduced through spironolactone (Chr. P. Klein), but is known to increase again after elimination of the medication. 3 had stage I-II hepatic encephalopathy. The Child-Pugh index was 9.8 +/− 2.4, that is, Child B. None of the 25 patients experienced gastrointestinal bleeding either prior to admission, or

later. All follow-up examinations included an oesophago-gastroduodenoscopy, for the most part carried out by one and the same physician to facilitate a uniform evaluation of the findings. At the time of admission, nine patients had stage III oesophageal varices, three, stage II-III, and the rest, stage II. In addition, annual virus serology was performed, and the most important liver parameters, in particular the urea synthesis rate, were measured as indicators of the size of functioning liver mass.

In all three groups, treatment comprised a diet containing 60 grams of protein, 300 grams of carbohydrates, 100 grams of fat = 2.200 kcal, and strict abstinence from alcohol. As basic medical therapy, lactulose (60–90 grams/day), and ammonia-reducing amino acids (6–9 grams ornithine-aspartate/day, (Hepamerz®) were administered. Patients suffering from haemochromatosis were regularly submitted to phlebotomy, which led to a histologically confirmed elimination of tissue iron, and remission of the cirrhotic transformation. In none of the 25 cirrhotics were sclerotherapy of the oesophageal varices, portasystemic shunting, or any other abdominal surgery performed. The long-term study was carried out in close cooperation with the respective family doctors. For that reason only, was it possible that all 25 patients with cirrhosis of the liver came to yearly stationary follow-up examinations over the period of 8–20 years (mean, 13 yr), and ambulatory controls every 1–3 years. Within the context of these visits was a regular ultra-sound examination of the liver, and abdomen to register the presence, and disappearance of ascites. All patients were instructed to collect their 24 hour urine, measure the quantity, and bring a sample along for laboratory evaluation. Urea-N, potassium, and sodium were then quantitatively measured. Through this combined supervision, plus regular analysis of plasma ammonia, large diet violations could be detected, and eliminated. Smaller ones were, naturally, always possible.

Results

The most important results are summarized on Fig. 1 to 5. The main reason for liver cirrhosis in Europe is alcohol, in our 25 patients as well. Therefore, is the influence of a long-term alcohol carence on portal hypertension and its sequelae to be examined. We determined the portal pressure by the method of wedged hepatic vein pressure, and found out that already after about 320 days of alcohol carence, which is about 10 months, the pressure of wedged hepatic vein decreased significantly (Fig. 1). The esophageal varices reduced as well, butnot significantly. Parallel hereto, the Child-Pugh-index improves significantly, and y-GT and serum transaminases diminish not significantly.

Fig. 2 shows the effect of continued alcoholic intake on portal hypertension, plasma ammonia and urea synthesis rate in a 68 yr old man suffering from decompensated alcoholic cirrhosis. Ascites, hepatic encephalopathy, and esophageal varices developed in the course of a 9 yr follow-up period (not drawn on Fig. 2).

In order to ameliorate the hepatic detoxification we started an approx. 13 yr long-term therapy with lactulose and ornithine-aspartate (Hepamerz®). Depending to the severity of portal hypertension this treatment as well is able to reduce the hyperammonemia significantly (Fig. 3). In this case, we administered daily over a period of 6–10 weeks initially 9 grams and later 6 grams of ornithine-aspartate. One patient died (No. 1) in hepatic encephalopathy, the other 9 ones improved clinically and biochemically. After we tested out the effect of ornithine-aspartate alone on biochemistry and clinic in liver cirrhosis we continued testing the effect on liver detoxification during a long-term period of 13 years. We experienced a significant decrease of plasma ammonia value to half

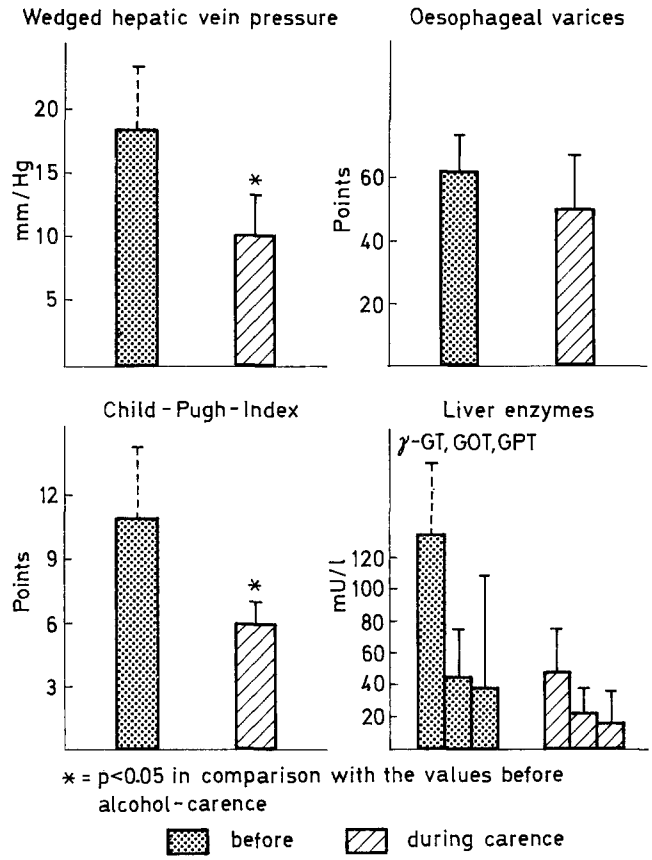

Fig. 1. Effect of alcohol-carence (320 days) on portal hypertension in alcoholic liver cirrhosis ($n = 18$)

of the initial value and a simultaneous significant increase of urea synthesis rate (Fig. 4).

Discussion

The favorable influence on portal hypertension in alcoholic cirrhosis after long-termed alcohol carence was described 30 years ago by T. B. Reynolds and C. Leevy et al. in the USA. Those authors as well measured the wedged hepatic vein pressure and found already after 9 months of strict alcohol abstinence a significant decrease of portal hypertension. Probably, these results were not thoroughly published because they remained rather unknown. However, they explained that the complete abstinence from alcohol in alcoholic cirrhosis is the most important basis for a medical treatment. The same principle is valid to eliminate hepatitis B- and hepatitis C-virus. A spontaneous seroconversion helps in about 25% of all cases to facilitate the therapeutical effectiveness.

An important subject in hemochromatosis and in iron-input induced liver cirrhosis is the elimination of iron by long-termed phlebotomies. R. Fischer, member of our hospital, could prove that long-termed phlebotomies do not only

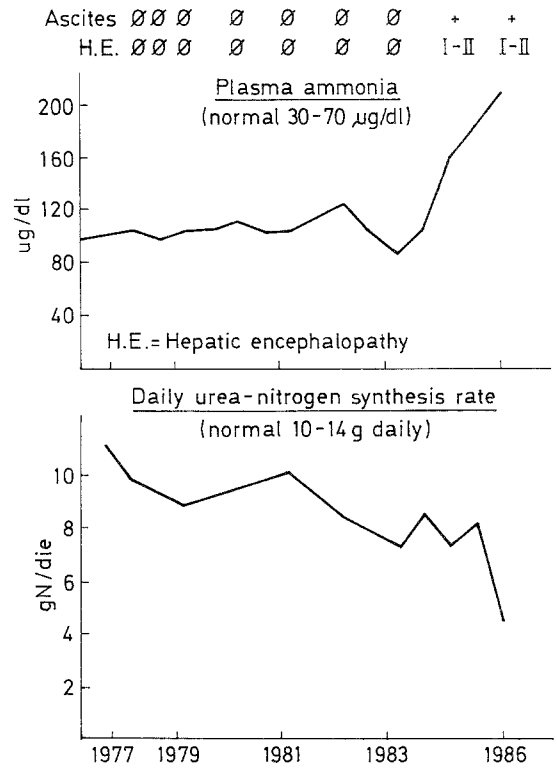

Fig. 2. Decompensation of alcholic liver cirrhosis (H.V.♂.68)

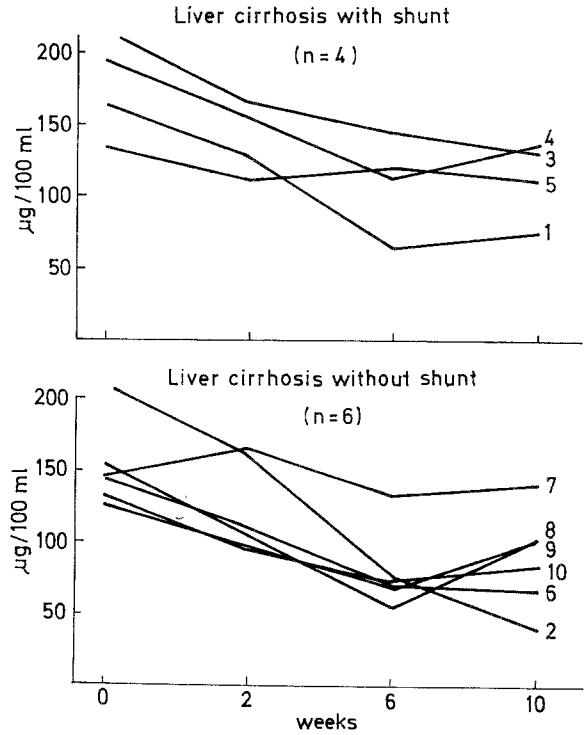

Fig. 3. Effect of ornithine-aspartate (Hepamerz®) on hyperammonemia in liver cirrhosis (Long-term therapy with 9–6 g/die)

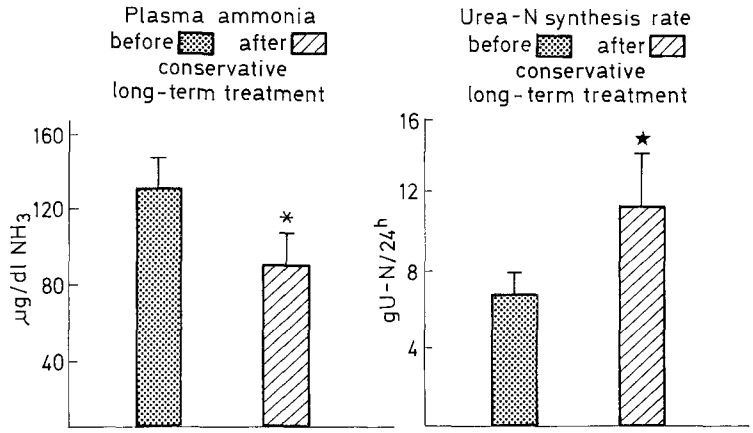

Fig. 4. Hepatic detoxification

remove completely iron in the liver but cause a clinical, morphological, and laparoscopic regression of liver cirrhosis.

Doubtlessly, the mentioned factors such as elimination of triggering causes of liver cirrhosis can be intensified by a medical basic treatment. The improvement of the intestinal detoxification by lactulose is one of the most important topics and is proven by controlled and double-blind studies (Müting et al., 1988; Conn et al. 1974). Therefore, the simultaneous administration of lactulose *and* ammonia-reducing amino acids, such as ornithine-aspartate, are suitable best for basic treatment of liver cirrhosis over a longer period. Fig. 4 demonstrates the effect on plasma ammonia and urea synthesis rate in 25 cirrhotics being treated basically over a period of approx. 13 years. Both parameters improved significantly. Much more important is the regression of the other sequelae of portal hypertension, such as esophageal varices, ascites and hepatic encephalopathy.

Fig. 5 summarizes the effectiveness of ornithine-aspartate on liver, muscular system and brain. Ammonia detoxification is improved in all 3 organs, whereby the coupling of ammonia with alpha-ketoglutaric acid plays a role as well.

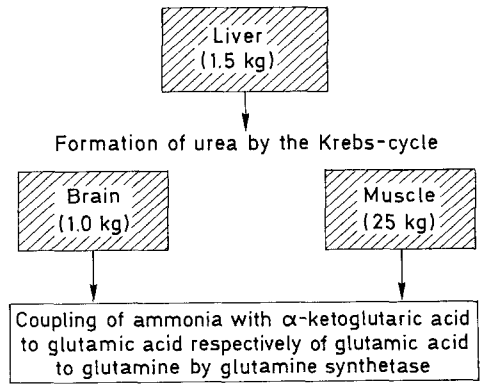

Fig. 5. Effect of ornithine-aspartate on ammonia detoxication

Precondition for the favorable effectiveness is – here once again – the complete abstinence from alcohol and the elimination of liver cirrhosis inducing factors.

References

1. Conn H, et al (1974) Lactulose in the treatment of chronic portal systemic encephalopathy. A prospective double-blind cooperative comparison of lactulose with neomycin. Gastroenterol 67: 784
2. Fischer R (1976) Klinik und Therapie der idiopathischen Haemochromatose. Erfahrungen bei 51 eigenen Fällen. Leber Magen Darm 6: 316–329
3. Klein Chr-P (1985) Spironolactone for treatment of portal hypertension in liver cirrhosis. A new therapeutical research. Dtsch Med Wochenschr 110: 1774–1776
4. Leevy CM, et al (1958) Observations on the influence of medical therapy on portal hypertension in hepatic cirrhosis. Ann Intern Med 49: 837–851
5. Müting D, et al (1988) Plasma ammonia and urea-N synthesis rate in human liver cirrhotics. In: Soeters PB, et al (eds) Advances in ammonia metabolism and hepatic encephalopathy. Elsevier, Amsterdam, pp 91–98
6. Müting D, et al (1988) Kontrollierte Studie über die Wirkung einer oral verabreichten ammoniaksenkenden Aminosäure (Ornithinaspartat) auf Leber- und Pankreasfunktion bei Leberzirrhosekranken. Therapiewoche 30: 5990
7. Reynolds TB, et al (1960) Spontaneous decrease in portal pressure with clinical improvement in cirrhosis. N Engl J Med 263: 734–739
8. Vilstrup H (1984) Urea synthesis in human. Preconditions of quantitation and relation to liver function. In: Kleinberger G, et al (eds) Advances in hepatic encephalopathy and urea cycle diseases. Karger, Basel, pp 141–146

Authors' address: Prof. Dr. D. Müting, Heinz Kalk-Krankenhaus, D-W-8730 Bad Kissingen, Federal Republic of Germany.

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