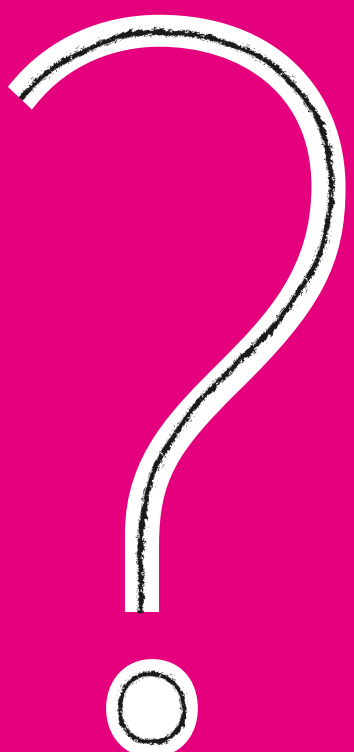
SCIENCE

ORAL L-ORNITHINE-L-ASPARTATE IN MINIMAL HEPATIC ENCEPHALOPATHY:

A RANDOMIZED, DOUBLE BLIND PLACEBO-CONTROLLED TRIAL

(ALVARES-DA SILVA ET AL, 2013)



Alvares-da-Silva MR et al. Hepatol Res. 2013 Sep 3. doi: 10.1111/hepr.12235.[1]

Hepa-Merz®
L-ornithine-L-aspartate

LOLA: SIGNIFICANT SYMPTOM REDUCTION...

Introduction

Overt (OHE) and minimal HE (MHE) share the same pathogenesis, involving reduced metabolism of ammonia leading to neurotoxicity, astrocytes oedema, neuroinflammation and impaired neutrophil function. The ability to perform daily activities along with quality of life and mortality are all affected. Treatment with L-ornithine-L-aspartate (LOLA) aims to control ammonia and improve symptoms. This is the first randomized, controlled trial investigating the efficacy and safety of LOLA in MHE.

LOLA is indicated for the treatment of disorders associated with hepatic detoxification impairment (e.g. liver cirrhosis) with symptoms of latent and manifest hepatic encephalopathy.[2]

Study

Objective

To evaluate the efficacy and safety of oral LOLA in controlling the symptoms of MHE.

Design

Prospective study in which patients with MHE associated with cirrhosis were randomized to 60-day oral LOLA (5 g t.i.d.) or placebo with 15-day appointments.

Patient population

64 cirrhotic patients were included – 63 (98.4%) with MHE. In 6/63, CFF was < 39Hz (9.52%), NH_3 was increased in 32 (50.8%), and 25% had abnormal quantitative EEG (qEEG).

Age, sex, scholarship, Child-Pugh (CP), model for end-stage liver disease (MELD), number connection test A/B (NCT-A/B), digit symbol substitution test (DSST), Critical Flicker Frequency test (CFF) and NH_3 were similar in both groups at the baseline.

Tests performed

Patients were assessed with psychometric tests (PHES) – NCT-A/B and DSST > 2 standard deviation, CFF, qEEG, arterial ammonia (NH_3), Beck's anxiety-depression forms and Liver Disease Quality Of Life (LDQOL).

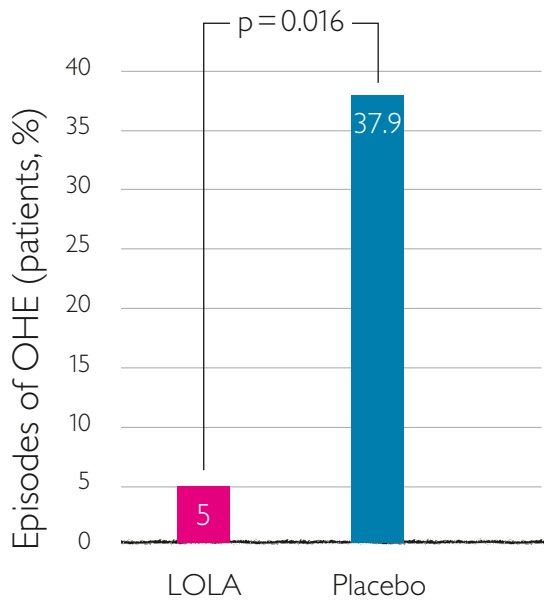
Patients were followed up 6 months after the end of the study to assess the efficacy and safety of LOLA and its prophylactic role in overt HE (OHE).

...AND PREVENTION OF FURTHER EPISODES OF OHE

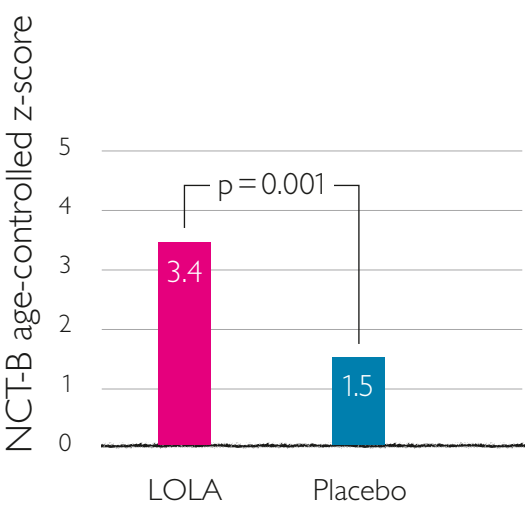
Results

- Treatment with LOLA led to a significant improvement in NCT-B age-controlled z-score (3.4 ± 3.4 vs. 1.5 ± 2.3; p = 0.01) and CFF (42.2 ± 5.8 vs. 45.2 ± 5.8; p = 0.02), comparing the first and the last visit.
- No serious adverse effects occurred.
- Patients taking LOLA also had significant improvement in liver function assessed by CP (p < 0.001).

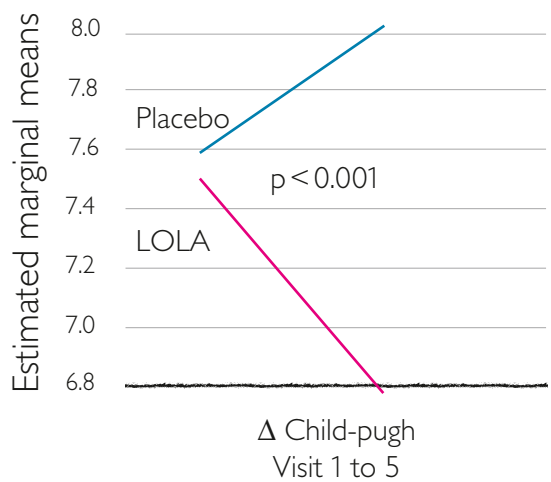
Significantly fewer episodes of OHE with LOLA at 6-months



Significantly improvement in NCT-B z-score with LOLA



Estimated marginal means of measure 1



Hepa-Merz®
L-ornithine-L-aspartate

LOLA CAN BE USEFUL IN THE PREVENTION OF FURTHER EPISODES OF OHE IN PATIENTS SUFFERING MHE

Conclusion

MHE is important to treat as patients can experience critical impairments in daily life, including driving skills, falls, memory loss and low quality of life. MHE is also prognostic for the later development of OHE. Treating MHE is challenging and there is as yet no consensus on the optimal dose of LOLA. In this study, a 60-day course of oral LOLA (5 g t.i.d.) was useful in preventing further episodes of OHE. LOLA therefore has an important prophylactic role in preventing further episodes of OHE. No study has previously reported this clinical benefit.

Hepa-Merz® Prescribing Information

Hepa-Merz® Granules. Active substance: L-ornithine-L-aspartate. **Composition:** One sachet with 5 g of Granules contains: **Active substance:** 3 g L-ornithine-L-aspartate. **Excipients:** citric acid, saccharin sodium, sodium cyclamate, povidone 25, fructose, flavorings, orange yellow S (E110). Note for diabetics: One sachet of Hepa-Merz® Granules contains 1.13 g of fructose (corresponds to approx. 0.11 BU). **Therapeutic indications:** Treatment of concomitant disease and sequelae due to impaired detoxification activity (e.g. in cirrhosis of the liver) with the symptoms of latent and manifest hepatic encephalopathy. **Contraindications:** Absolute: Hypersensitivity to L-ornithine-L-aspartate, orange yellow S or any of the other excipients. Severely impaired renal function (renal insufficiency). A serum creatinine value over 3 mg/100 ml can be used as a guideline value. Relative: Pregnancy and lactation: No clinical data are available relating to intake of Hepa-Merz® Granules during pregnancy. No exhaustive animal studies have been performed for L-ornithine-L-aspartate, to investigate its toxicity in relation to reproduction. Administration of Hepa-Merz® Granules during pregnancy should therefore be avoided. If, however, treatment with Hepa-Merz® Granules is considered necessary, careful consideration should be given to the benefit versus risk ratio. It is not known whether L-ornithine-L-aspartate is excreted into the breast milk. Administration of Hepa-Merz® Granules should therefore be avoided during lactation. If, however, treatment with Hepa-Merz® Granules is considered necessary, careful consideration should be given to the benefit versus risk ratio. **Undesirable effects:** Uncommon (≥ 1/1000 to < 1/100): Nausea, vomiting, stomach ache, flatulence, diarrhea. Very rare (< 1/10000): Pain in the limbs. These undesirable effects are usually transient and do not require withdrawal of the medicine. Orange yellow S (E110) can trigger allergic reactions. **Warnings:** Hepa-Merz® Granules contain fructose. Patients with rare hereditary problems of fructose intolerance should not take this medicine. **Further precautions:** As a result of the disease, the ability to drive and operate machinery may be impaired during treatment with L-ornithine-L-aspartate.

Hepa-Merz® Infusion concentrate. Active substance: L-ornithine-L-aspartate. **Composition:** One ampoule of 10 ml contains: **Active substance:** 5 g L-ornithine-L-aspartate. **Excipients:** Water for injections. **Therapeutic indications:** Latent and manifest hepatic encephalopathy. **Contraindications:** Absolute: Hypersensitivity to L-ornithine-L-aspartate. Severe renal impairment (renal failure). A serum creatinine level in excess of 3 mg/100 ml can be taken as a guide. Relative: Pregnancy and lactation: There are no clinical data available on the use of Hepa-Merz® Infusion concentrate in pregnancy. L-ornithine-L-aspartate has been investigated for reproduction toxicity only to a limited extent in experimental animal studies. The administration of Hepa-Merz® Infusion concentrate in pregnancy should therefore be avoided. If treatment with Hepa-Merz® is nevertheless thought to be necessary, the benefits and risks should be carefully assessed. It is not known whether L-ornithine-L-aspartate passes into breast milk. Administration of Hepa-Merz® should therefore be avoided during lactation. If treatment with Hepa-Merz® is nevertheless thought to be necessary, the benefits and risks should be carefully assessed. **Undesirable effects:** Uncommon (≥ 1/1000 to < 1/100): Nausea. Rare (≥ 1/10000 to < 1/1000): vomiting. Frequency not known (frequency cannot be estimated from the available data): hypersensitivity, anaphylactic reaction. Generally however, the gastrointestinal symptoms are transient, and do not necessitate discontinuation of treatment. They disappear on reduction of the dose or the infusion rate. **Further precautions:** Hepa-Merz® concentrate for solution for infusion can be mixed with the usual infusion solutions. So far no peculiarities have been observed with regard to miscibility. However, the ampoules should be admixed to the infusion solution only immediately before application. At high doses of Hepa-Merz® Infusion concentrate, serum and urine urea levels should be monitored. If liver function is substantially impaired, the infusion rate must be adjusted to the individual patient in order to prevent nausea and vomiting. Depending on the underlying disease, the ability to drive and operate machines may also be impaired on treatment with L-ornithine-L-aspartate. Hepa-Merz® Infusion concentrate must not be injected into an artery. Status: January 2013. Merz Pharmaceuticals GmbH, 60048 Frankfurt.

Reference: 1. Alvares-da-Silva MR, et al. Hepatol Res. 2013 Sep 3. doi: 10.1111/hepr.12235. **2.** Specialist information Hepa-Merz® Infusion Concentrate. Specialist information Hepa-Merz® Granules. Hepa-Merz® Summary of Product Characteristics.

For more information, visit **www.merz.com**