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L-Ornithine L-Aspartate for Prevention and Treatment of Hepatic Encephalopathy in Patients with Cirrhosis

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Abstract

In cirrhosis, the loss of metabolic capacity of periportal and perivenous hepatocytes coupled with the development of portal-systemic shunting frequently results in severe hyperammonemia. Molecular Imaging and Spectroscopic techniques reveal increases in the cerebral metabolic rate for ammonia and increased brain glutamine as a function of the severity of hepatic encephalopathy [HE]. L-Ornithine L-Aspartate [LOLA] is effective for the lowering of blood, muscle and brain ammonia and does so via three independent mechanisms namely [i] the stimulation of ammonia removal via the urea cycle in residual hepatocytes, [ii] prevention of hepatocellular damage due to the production of antioxidants [glutathione, glutamine] and [iii] the prevention of muscle wasting [sarcopenia] thus protecting the ammonia-detoxification pathway via muscle glutamine synthesis. Results of RCTs, systematic reviews and meta-analyses provide evidence for the efficacy of LOLA for the prevention and treatment of HE in all its forms [MHE, OHE, episodic HE, post-TIPSS HE] and for primary, secondary and post-TIPSS prophylaxis.

Keywords: L-ornithine L-aspartate; LOLA; Hepatic encephalopathy; Cirrhosis; Treatment; Prevention; Prophylaxis; Ammonia; Hepatoprotection; Sarcopenia; Combination therapy

Introduction

Hepatic encephalopathy [HE] in patients with cirrhosis manifests clinically as a broad spectrum of neurological and/or psychiatric abnormalities occurring either episodically associated with one of a series of well-recognised precipitating factors or with a chronic persistent course due to extensive portal-systemic shunting. Clinically manifest HE, also referred to as overt HE [OHE], is graded in severity using Westhaven Criteria whereas mild impairments known as minimal HE [MHE] are recognised using a series of psychometric test procedures. The onset of OHE in cirrhosis heralds a poor prognosis with negative impact on health-related quality of life and patient survival.

Ammonia: Key Factor in the Pathogenesis of HE in Cirrhosis

Patients with cirrhosis invariably go on to develop portal-systemic shunting that, in combination with reductions of the metabolic capacities of periportal and perivenous hepatocytes to detoxify ammonia, leads to profound hyperammonemia [1] of sufficiently high concentration to cause impairments of cellular energy metabolism and neurotransmitter homeostasis that form the basic mechanisms responsible for the pathogenesis of HE. Arterial blood and brain concentrations of ammonia are increased several-fold in cirrhosis and dynamic $^{13}NH_3$ -Positron Emission Tomography [PET] studies reveal significant increases in cerebral metabolic rate for ammonia [CMRA] in HE patients [2]. Removal of excess ammonia in brain relies exclusively on its incorporation into the molecule of glutamine via the enzyme glutamine synthetase [GS] and ^{1}H-Magnetic Resonance Spectroscopy reveals that brain glutamine concentrations are significantly increased as a function of the severity of OHE in patients with cirrhosis [3].

Ammonia-Lowering Action of L-Ornithine L-Aspartate [LOLA] in Cirrhosis

LOLA is a stable salt of its naturally-occurring constituent amino acids L-Ornithine and L-Aspartate both of which are metabolically active as

intermediates in the urea and tricarboxylic acid cycles respectively by virtue of which they have the potential, acting synergistically to lower blood ammonia. Results of a systematic review with meta-analysis of 8 randomized placebo-controlled trials [709 patients with cirrhosis] confirmed the efficacy of LOLA for the lowering of circulating ammonia as shown in Figure 1. Intravenous and oral formulations of LOLA were equally effective [4] (Figures 1 & 2).

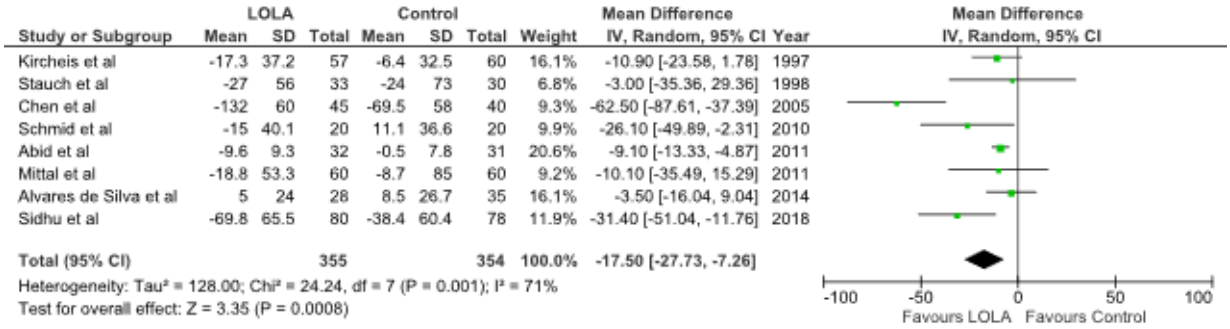

Figure 1: Efficacy of LOLA [iv or oral formulation] for the lowering of blood ammonia in patients with cirrhosis. Findings are presented as Forest plots of data from pooled effect of LOLA or placebo. Identity of individual RCT is indicated by first author name and year. Results are expressed as MD: -17.50 [95%CI: -27.73, -7.26], test for overall effect: Z=3.35, p=0.0008 [4].

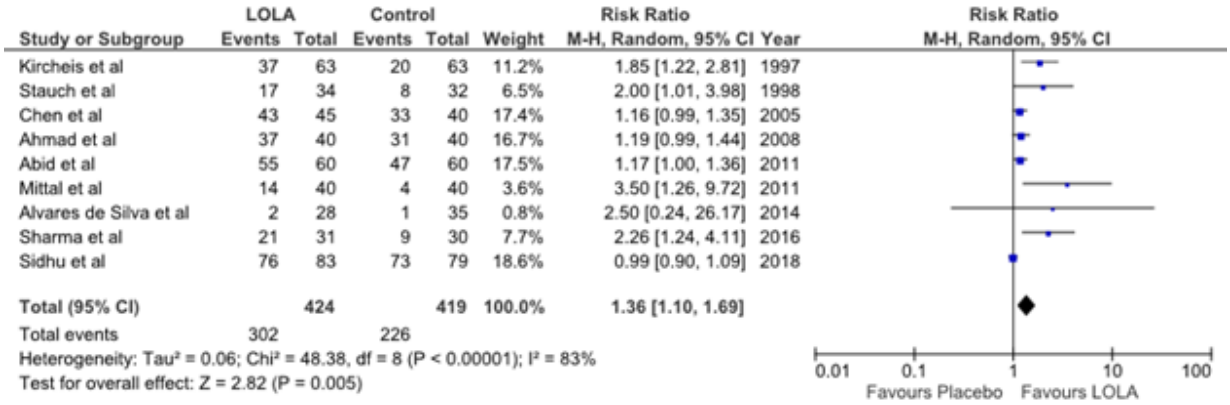

Figure 2: Efficacy of LOLA [iv or oral formulation] for improvement of mental score / HE grade in patients with cirrhosis. Findings are presented as Forest plots of data from pooled effect of LOLA or placebo. Results are expressed as RR: 1.36 [95%CI: 1.10, 1.69], test for overall effect: Z=2.82, p=0.005 [4].

Results of both basic and clinical research endeavours continue to identify mechanisms responsible for the beneficial effects of LOLA. Novel insights include the identification of metabolic ammonia scavenger actions of LOLA involving activation of the urea cycle and of multiple transaminase reactions. In addition, there is evidence to support the notion that LOLA has hepatoprotective properties via the synthesis of antioxidants. In addition, there is increasing evidence that LOLA prevents sarcopenia in cirrhosis going on to stimulate skeletal muscle to participate in removal of excess ammonia via glutamine production.

a. LOLA: a potent bimodal metabolic ammonia scavenger

Reduction of hyperammonemia in cirrhosis depends largely upon the activation of well-characterised key metabolic processes whereby ammonia is incorporated into the molecule of urea by residual hepatocytes in the damaged liver that continue to express the constituent enzymes of the urea cycle of which L-Ornithine is an active intermediate. In addition, both L-Ornithine and L-Aspartate are substrates for transaminases with the potential to supply equimolar concentrations of glutamate the obligate substrate for GS in a metabolic pathway leading to ammonia incorporation into the molecule of glutamine. This ammonia-removal pathway is available in multiple locations including residual perivenous hepatocytes as well as in skeletal muscle and brain. Other agents described as specific ammonia scavengers have also been developed or repurposed from other indications but comparison of efficacies with that of LOLA reveal that LOLA is superior both in terms of efficacy for ammonia lowering and for improvement of mental state [5].

b. Hepatoprotective properties of LOLA

Results of a study of 314 patients with cirrhosis revealed that treatment with LOLA led to significant improvements in circulating transaminases and bilirubin that were consistent with reductions in hepatic damage suggestive of a hepatoprotective action [6]. These results were confirmed and extended in subsequent results of controlled clinical trials in which improvements in liver enzymes and bilirubin were reported an addition to improvements in prothrombin times [7], Child-Pugh and MELD scores [8] were observed. Moreover, improvements in MELD were also described in a trial of the efficacy of LOLA for the treatment of post-TIPSS HE [9]. A review of these findings of apparent hepatoprotective actions of LOLA in cirrhosis was subsequently reported where probable mechanisms responsible for beneficial effects of LOLA were summarised that included increases in production of metabolites with anti-oxidant actions that included glutamine and glutathione from L-Ornithine via glutamate and/or the increased production of nitric oxide via L-Arginine with the potential to improve hepatic microcirculation [10].

c. Prevention of sarcopenia in cirrhosis leading to improved muscle function and removal of ammonia following treatment with LOLA

It is well established that in conditions of liver failure, the pattern of inter-organ trafficking of ammonia is modified so that skeletal muscle takes over from the liver for the effective removal of excess ammonia by increased synthesis of glutamine via glutamine synthetase [GS]. This changeover is catalysed by a post-translational increase in expression of the GS gene in skeletal muscle [11]. Unfortunately,

this process is jeopardised by damage to skeletal muscle known as sarcopenia. Characterized by significant losses of skeletal muscle mass, function and strength, sarcopenia is encountered with comparable frequency and may even be a risk factor for the increased prevalence of HE in patients with cirrhosis [12]. Sarcopenia is also associated with poor outcomes including health-related quality of life and with the emergence of complications and survival both prior to and post-liver transplantation [13]. Studies in human skeletal muscle preparations exposed to ammonia manifest significant activation of molecular signalling systems known to contribute to the pathogenesis of sarcopenia in cirrhosis. For example, exposure to ammonia results in the up-regulation of myostatin an established inhibitor of muscle protein synthesis leading to increased autophagy, a cardinal feature of sarcopenia [14].

Evidence of skeletal muscle autophagy has also now been reported in patient material confirming that such changes contribute to sarcopenia in cirrhosis [15]. Based on these findings it has been proposed that a "vicious cycle" occurs in cirrhosis in which hyperammonemia resulting from reduced hepatic ammonia removal as urea and/or glutamine together with portal-systemic shunting results in muscle dysmetabolism and autophagy that effectively robs the inter-organ ammonia trafficking system of its "back-up" role for ammonia removal in the form of glutamine by skeletal muscle.

Fortunately, help was at hand. Insights into pathophysiology of sarcopenia in cirrhosis came from investigations in cultured murine myotubes and subsequently in muscle from rats with hyperammonemia due to end-to-side portacaval anastomosis [a model of HE] revealed increased expression of myostatin as well as other autophagic markers. Treatment with LOLA and an antibiotic resulted in significant reductions of circulating and muscle ammonia together with improved lean body mass, grip strength, muscle mass and muscle fibre diameter [16]. Translation to the clinic took the form of a placebo-controlled metabolic study in percutaneous biopsies of anterior *tibialis* muscle from 16 patients with cirrhosis and marked sarcopenia demonstrating that LOLA treatment improved muscle protein synthesis rates [17].

Efficacy of LOLA for the treatment of HE in cirrhosis: review of the evidence

The efficacy of LOLA for the treatment of both MHE and OHE [improvement of mental state] in cirrhosis was first described in a systematic review with meta-analysis of the same trials in which ammonia lowering was demonstrated [Figure 2a] [4] and similar benefits of LOLA for improvements in mental state/HE grade were subsequently confirmed in two independent meta-analyses where again both intravenous and oral formulations of LOLA were effective [18,19].

Combination therapy involving for the treatment of high-grade OHE in cirrhosis

A novel RCT compared the efficacy of combination therapy consisting of lactulose, rifaximin and iv LOLA for the treatment of acute high-grade OHE [grades 3,4]. Treatment with the three-agent combination resulted in significant concomitant reductions of hyperammonemia, improvements of HE grade, lower time to recovery from HE and reduced 28-day mortality ($p = 0.001$) compared to lactulose and rifaximin [20].

Efficacy of LOLA for the prevention of OHE in cirrhosis

Given the negative impact on cognitive function, quality of life and liver transplant outcomes in addition to the elevated risk for future HE episodes, effective interventions aimed at the prevention of OHE are constantly under development with considerable success. LOLA is effective in a range of clinical presentations including primary OHE prophylaxis following acute variceal bleeding [21] as well as for the prevention of OHE recurrence [secondary prophylaxis] [22] and for post-TIPSS prophylaxis [9]. LOLA is also effective for the prevention of the deterioration of MHE to OHE in patients with cirrhosis according to evidence provided in three separate RCTs [7,8,19].

Conclusion

Three distinct actions of LOLA relating to activation of urea cycle and transaminases lead to increased incorporation of ammonia into the molecules of urea and glutamate/glutamine with concomitant lowering of blood, muscle and brain ammonia. Secondly, Conversion of its constituent amino acids into antioxidants and nitric oxide, LOLA has the potential to mitigate hepatocellular damage due to oxidative stress and to improve hepatic microcirculation. Such changes are likely responsible for the LOLA-induced improvements in urea and glutamine synthesis by residual periportal and perivenous hepatocytes respectively resulting in the effective lowering of blood ammonia and improved HE grade observed in patients with cirrhosis. In addition, current evidence supports the notion that LOLA largely corrects the sarcopenia associated with cirrhosis [that itself, like HE, is largely due to ammonia exposure] freeing the muscle to participate in ammonia removal as glutamine in concert with the residual perivenous hepatocytes of the damaged liver.

Results of randomised clinical trials, systematic reviews and meta-analyses continue to provide high-grade evidence in support of the efficacy of LOLA for both the prevention and treatment of HE in cirrhosis across a wide range of clinical presentations including MHE and OHE as well as for Primary, secondary and post-TIPSS prophylaxis.

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