Hyperammonemic hepatic encephalopathy management through L-ornithin-L-aspartate administration in dogs

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Seventeen dogs were treated with L-ornithin-L-aspartate (LOLA; experimental group). Three dogs were treated with lactulose recognized therapy (control group). Following LOLA administration, 15 dogs experienced a significant decrease in ammonia level (p < 0.05) and showed clinical signs of improvement. However, there were no clinical signs of improvement in two dogs, even though the ammonia level decreased. Conversely, the clinical signs of the control group also improved and the ammonia level decreased, although these changes were not significant (p > 0.05). These results suggest that LOLA is an effective drug to treat hyperammonemia in veterinary medicine.

Keywords: L-ornithin-L-aspartate, dogs, hepatic encephalopathy, hyperammonemia

The reduction of ammonia detoxification in the liver is the most important cause of hyperammonemia [5,14]. Ammonia is detoxified via conversion to urea and glutamine in hepatic cells. When hepatic failure occurs, the liver can no longer detoxify ammonia [2,4,5,14]. These conditions are common in the veterinary field [9]. The pathogenesis of hepatic encephalopathy (HE) has not yet been fully elucidated, although it is known that increased ammonia concentration in the blood contributes to its pathogenesis [6].

The goal of treatment of HE is restoration of normal neurologic function of patients by decreasing hyperammonemia. Currently, hyperammonemia is medically managed by protein restrictions, lactulose and antibiotic treatment. Ammonia detoxification in the metabolic organ is currently viewed as more important than protein restriction [8,10,15], necessitating that a new treatment be developed. In this experiment, we administered L-ornithine-L-aspartate (LOLA), which is currently used only in human medicine, to treat hyperammonemia. LOLA promotes ammonia detoxification by stimulating disrupted urea and glutamine synthesis [1,7,11,13]. In this study, we administered LOLA to dogs with hyperammonemic HE and evaluated its efficacy.

A total of 20 dogs were recruited for this study, among which the owners of 17 gave permission for LOLA administration (experimental group). The other three dogs were treated with the lactulose recognized therapy (control group). The experimental group met the criteria. Including criteria comprised dogs afflicted with hyperammonemic HE caused by liver diseases and LOLA as the first choice to control hyperammonemia. Other including criteria were that the ammonemia level immediately before and 24 h after LOLA administration was assessed.

The experimental group included one Schnauzer, nine Malteses, three Shih Tzus, two Yorkshire Terriers, one Cocker Spaniel and one Golden Retriever. Six were intact females, four were spayed females, one was an intact male and six were castrated males. The mean age was 8.7 years. The control group included one Maltese, one Shih Tzu, and one Bichon Frise. One dog in the control group was a spayed female and two were castrated males. The mean age was 5.3 years.

Diagnostic work up was conducted by physical and neurological examination, complete blood count and chemical analysis, X-ray, ultrasound, and fine needle biopsy. With this diagnostic work up, we confirmed the subjects to have hyperammonemic HE (FUJI DRI-CHEM analyzer 4000i; FUJIFILM Corporation, Japan) with liver disease (11 chronic hepatitis, 8 portosystemic shunt, 1 acute liver failure). The degree of hepatic encephalopathy was graded according to Meyer’s criteria (Table 1) [9]. In this
Table 1. Grading scheme for hepatic encephalopathy

| HE grade | Clinical sign                                                                 |
|----------|-------------------------------------------------------------------------------|
| 0        | Normal                                                                        |
| I        | Reduced motility and/or mild apathy                                           |
| II       | Severe apathy and/or mild ataxia                                              |
| III      | Salivation, severe ataxia, head pressing, apparent blindness, and/or circling |
| IV       | Seizures and/or nearly complete to complete unresponsiveness, i.e., stupor-coma |

HE, hepatic encephalopathy.

study, grade I and II were classified as mild HE and grade III and IV were classified as severe HE. Among the 17 dogs, eight suffered from severe HE and nine from mild HE.

The experimental group received LOLA (Hepa-Merz Gel; Hanwha Pharma, Korea). Common doses of LOLA were 0.154-0.616 g/kg/day and the maximum dose was 1.232 g/kg/day. In dogs with severe HE, LOLA was administered at 0.154 g/kg/h for the first 4 h and 0.03 g/kg/h for the remaining 20 h to meet the maximum dose (1.232 g/kg/day). Dogs suffering from mild HE were administered LOLA (0.616 g/kg/day) for one day intravenously. The control group received lactulose at 2.5-15 mL every 8 h via enema.

With LOLA intravenous administration, the level of ammonemia decreased and the clinical signs of severe HE improved from grade III or IV to grade 0 or I. The level of ammonemia in seven dogs with mild HE also decreased and the clinical signs improved from grade I to grade 0. At 24 h after LOLA administration, the ammonemia level decreased with statistical significance in both mild HE and severe HE (mild HE, *p < 0.05; severe HE, *p < 0.01) (Fig. 1). However, there were no clinical signs of improvement in the two dogs with mild HE occurring from acute liver failure and portosystemic shunt, even though the ammonemia level decreased. With LOLA administration, there were no obvious side effects secondary to administration. On the other hand, all animals in the control group suffered from severe HE. Following lactulose administration, the clinical signs of this group also improved from grade IV to grade I or II and the ammonemia level decreased, although this decrease was not statistically significant (*p > 0.05).

The changes in ammonemia level from before LOLA administration to 24 h after LOLA administration were analyzed by the Wilcoxon signed-rank test. *P values were two-tailed and statistical significance was accepted for *p values less than 0.05.

The liver failures with HE implications are one of the major disorders in the veterinary field [3]. However, this is the first study to investigate trials of LOLA administration to improve liver functions in veterinary patients. Therefore, the results presented herein open the door for a new therapy for dogs with HE.

There was no known dosage applicable to dogs because this is the first application in the veterinary field. The dosage was converted from human to dog according to the Reagan-Shaw method [12]. Side effects of LOLA in humans include vomiting with rapid infusion. However no side effects were observed in dogs in the present study.

Overall, the results of this study suggest that LOLA has efficacy in dogs with HE, but further studies are required to investigate its administration with other standard therapies.

Acknowledgments

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2014R1A1A1004339), BK21 PLUS Program for Creative Veterinary Science Research and the Research Institute for Veterinary Science, Seoul National University.

Conflict of Interest

There is no conflict of interest.

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