Intravenous Arginine Dramatically Improved Hyperammonemia in a Patient with Late-onset Ornithine Transcarbamylase Deficiency

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Kodama, H., Mori, Y., Kubota, K., Itsuka, T., Nakazato, Y. and Abe, T. Intravenous Arginine Dramatically Improved Hyperammonemia in a Patient with Late-onset Ornithine Transcarbamylase Deficiency. Tohoku J. Exp. Med., 1996, 180 (1), 83–86 —— We describe a 12 year-old male patient with late-onset ornithine transcarbamylase deficiency, in whom infusion of arginine alone dramatically improved intercurrent hyperammonemia. The plasma glutamine level also decreased while the urea nitrogen level increased with arginine infusion, indicating that accumulated nitrogen was metabolized to urea in response to the arginine infusion. —— ornithine transcarbamylase deficiency; hyperammonemia; arginine infusion; carnitine; sodium benzoate

Ornithine transcarbamylase (OTC) deficiency, one of urea cycle diseases, is characterized by hyperammonemia. The inheritance is an X-linked dominant trait, and male patients with OTC deficiency usually suffer from fatal hyperammonemia during the neonatal period. However, some male patients have been reported to be partial OTC deficiency, because of residual enzyme activity. These male patients and female patients with OTC deficiency show various clinical courses. Since the age of onset and the severity of the disease vary from case to case, the disease is usually termed late-onset OTC deficiency. Patients with late-onset OTC deficiency often suffer from intercurrent hyperammonemia. Brusilow et al. (1984, 1995) recommended an intravenous infusion containing sodium benzoate, sodium phenylacetate and arginine-HCl as a treatment for this hyperammonemia. However, sodium benzoate and sodium phenylacetate intravenous infusions have not been approved as either commercial or orphan drugs.

We report here that an infusion of arginine alone dramatically improved intercurrent hyperammonemia in a 12-year-old boy with late-onset OTC deficiency.

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**Case Reports**

The patient had had several episodes of hyperammonemia since the age of 10 months. A liver biopsy at 2 years of age revealed that his liver OTC activity at pH 8 was about 10\% of the control level, while the activity at pH 10 was 60\%. In other words, he was suffering from the second group of the five different types of OTC deficiency classified by Briand et al. (1982). His clinical course and a detailed study of the enzyme levels in his liver specimen have been previously reported (Ushijima et al. 1985). Since two years of age he has been treated with a protein restricted diet (about 1 g protein/kg/day). Until the age of 12 years, he had had only two episodes of mild hyperammonemia that were easily improved by oral administration of sodium benzoate. He was admitted to our hospital because of vomiting and hyperammonemia (plasma ammonium level, 259 µg/100 ml), after an upper respiratory infection, at the age of 12 years. His height, weight and mental development were normal. The blood erythrocyte and leukocyte counts and the serum levels of electrolytes and proteins were normal; c-reactive protein was negative. Serum levels of aspartate and alanine aminotransferase were 64 and 54 IU/liter, respectively. At first, he was treated with a 7.5\% glucose infusion. On the second day, oral administration of sodium benzoate was added to his treatment. Carnitine, kanamycin and lactulose were also orally administered, beginning on the 4th day of hospitalization. However, the plasma ammonium level did not decrease. The sodium benzoate treatment was stopped on the 5th hospital day because the serum alanine aminotransferase level increased to 110 IU/liter. On the 6th hospital day, the plasma ammonium level increased to 491 µg/100 ml and the symptoms of hyperammonemia, such as headache and vomiting, became severer. Although the serum arginine level was normal, a 10\% arginine-HCl solution was intravenously started at a rate of 0.6 ml/kg/hr. Surprisingly, 1 and 5 hr after the start of the arginine infusion, the plasma ammonium level decreased to 141 and then to 71 µg/100 ml, respectively. Fig. 1 shows the effect of intravenous arginine on plasma levels of ammonium and urea. At the same time, the symptoms disappeared immediately. When the arginine infusion was stopped for 2 hr on the following day, the plasma ammonium level increased, along with a reappearance of headache. After arginine infusion was resumed, the plasma ammonium level gradually decreased to the normal level. The level remained normal after the arginine infusion was discontinued on the 12th hospital day. The plasma levels of urea as well as the arginine and ornithine increased in response to intravenous arginine, while the plasma glutamine level decreased (Fig. 2). He showed no adverse effects from the arginine infusion.

**Discussion**

Arginine has been reported to be an indispensable amino acid for patients with inborn errors of ureagenesis (Brusilow 1984). It also activates N-
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Fig. 1. Effects of intravenous arginine in a 12-year-old boy with late-onset ornithine transcarbamylase deficiency.

Fig. 2. Effects of intravenous arginine on plasma levels of glutamine (○—○), arginine (●—●), ornithine (△—△) in this patient. The vertical lines represent the normal ranges of plasma amino acid levels. Normal range of each substance is indicated.

acetylglutamate synthetase, resulting in activation of the urea cycle (Kawamoto et al. 1985). Therefore, oral supplementation of arginine has been recommended for these patients. (Batshaw et al. 1982; Brusilow and Horwich 1995). Moreover, an
intravenous infusion containing sodium benzoate, sodium phenylacetate and arginine-HCl has been recommended as a treatment for intercurrent hyperammonemia in patients with late-onset OTC deficiency. However, there are few patients treated with arginine infusion alone. Hyperammonemia in our case was dramatically improved by arginine infusion. Carnitine was also orally administered during arginine infusion. However, carnitine administration did not appear to have any effect on the hyperammonemia, because plasma ammonium levels were not decreased by the treatment with carnitine before arginine infusion. Most patients with OTC deficiency have a secondary carnitine deficiency, and the carnitine administration has been reported to decrease the frequency of hyperammonemic attacks in these patients (Ohtani et al. 1988). However, whether or not carnitine administration acts to decrease the serum ammonia level during hyperammonemic attacks remains unknown. In our case, carnitine as well as kanamycine and lactulose seemed to be of no effect in terms of improving hyperammonemia. The effects of intravenous arginine on plasma levels of urea and amino acids in our patient indicate that the accumulated nitrogen was metabolized to urea via the urea cycle. Our experience shows that intravenous arginine is beneficial for treating hyperammonemia in patients with late-onset OTC deficiency.

References


