Case Report

SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
Volume 6: 1–4

DOI: 10.1177/2050313X18778730
journals.sagepub.com/home/sco
SAGE

L-citrulline supplementation in the treatment of pulmonary hypertension associated with bronchopulmonary dysplasia in preterm infant: A case report

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Abstract

Introduction: the aim of this case report is to present that oral L-citrulline supplementation may attenuate chronic pulmonary hypertension and reduce oxygen requirement in infants with severe bronchopulmonary dysplasia.

Important clinical findings: a boy, with a birth weight of 700 g, born by cesarean section after 25 weeks of pregnancy complicated with preeclampsia, was admitted to the neonatal intensive care unit. He was ventilatory dependent for the next 3 months with significantly increased oxygen requirements. A severe stage of bronchopulmonary dysplasia, complicated with increased pulmonary vascular resistance, was diagnosed. Treatment with inhaled nitric oxide and oral sildenafil was included in the therapy of chronic pulmonary hypertension. The results of screening echocardiograms and increased plasma brain natriuretic peptide concentrations, suggested right ventricle dysfunction.

The main intervention: at the beginning of the sixth month of hospitalization, oral supplementation of L-citrulline in a single dose of 150 mg/kg/day was introduced and continued for 70 days. During the first 3 weeks after L-citrulline was started, the patient was weaned from mechanical ventilation and he was never intubated again until he was discharged. Plasma brain natriuretic peptide concentrations decreased significantly during the first month of L-citrulline administration and became stable until the termination of L-citrulline supplementation. At discharge, the patient required 22%–25% concentration of oxygen supplemented intermittently, exclusively during feeding.

Conclusion: these results indicate that L-citrulline supplementation may deserve coverage as an additional, potentially beneficial alternative in the prophylaxis or therapy of chronic pulmonary hypertension in newborns.

Keywords

Bronchopulmonary dysplasia, pulmonary hypertension, newborn infant, L-citrulline

Date received: 20 January 2018; accepted: 1 May 2018

Introduction

With an increasing percentage of extremely immature infants surviving in the last 10–15 years, bronchopulmonary dysplasia (BPD) has become one of the most frequent diagnoses in neonates. Approximately 25% of preterm infants with moderate and severe BPD are developing pulmonary hypertension (PH) as a result of excessive inflammatory response, oxygen toxicity, and stretch injury.[1] Together with alveolar hypoxia, these factors lead to endothelial dysfunction, resulting in an augmented resistance in pulmonary arteries, which increases the risk of mortality.

Supplemental oxygen therapy is the common treatment option for PH associated with BPD and target systemic arterial oxygen saturations are commonly maintained between 95% and 97% for all premature infants with diagnosed PH. However, when the concentration of administered oxygen exceeds 80%, it may increase the activity of

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phosphodiesterase-5 (PDE-5), which reduces the amount of cyclic-Guanyl-Monophosphate (c-GMP) and in consequence, increases resistance in the pulmonary arteries.[2] A variety of experience is reported for the oral administration of PDE-5 inhibitor—sildenafil, which improves pulmonary arteries perfusion in infants with BPD complicated by chronic PH.[3] One treatment of PH associated with BPD is inhaled nitric oxide (iNO) but it needs application of invasive ventilatory support, which prolongs stress and increases lung injury caused by mechanical ventilation. The use of potent intravenous vasodilators, such as epoprostenol, may be limited due to the adverse effects of hypotension or intrapulmonary right-to left pulmonary shunting, resulting in consecutive hypoxemia.

There is some preliminary data in newborn animals to suggest that the administration of exogenous L-citrulline may be of benefit in the context of neonatal chronic PH. In the newborn animal models of both chronic hyperoxia-induced and chronic hypoxia-induced PH, it has been shown that oral or subcutaneous treatment with L-citrulline increases pulmonary vascular NO production, attenuates the development of increased pulmonary arteries resistance and reduces right ventricular hypertrophy.[4,5] Also, the evidence of improved endothelial function was found in adult patients with diastolic heart failure after treatment with oral L-citrulline for 60 days.[6] In children undergoing cardiopulmonary bypass, postoperative PH did not develop when plasma citrulline concentrations were greater than 37 µm with oral citrulline supplementation.[7] One possible explanation for the beneficial effects of L-citrulline in chronic PH suggests that treatment with L-citrulline buffers pulmonary arterial endothelial cells, being in hypoxic conditions, against the reduction of endothelial nitric oxide synthase (eNOS) dimeric to monomeric forms ratio.[8] The dominance of eNOS dimeric forms causes an increase in NO production and reduces superoxide generation.

Patient information

A boy, with a birth weight of 700 g, by cesarean section after 25 weeks of pregnancy complicated with preeclampsia, was admitted immediately after birth to the neonatal intensive care unit. The administration of three consecutive doses of surfactant allowed the reduction of oxygen requirement from 80%–90% to 40%–45%. However, despite treatment with a hydrocortisone, introduced in the fourth week of life and given during the next 10 consecutive days, he remained ventilatory dependent with oxygen requirements that fluctuated from 45% to 75%. A severe stage of BPD, complicated with increased pulmonary vascular resistance was diagnosed by echocardiographic examination. Apart from recurrent administration of iNO, also a phosphodiesterase-5 inhibitor, oral sildenafil was included in the treatment of chronic PH. The results of screening echocardiograms and increased plasma brain natriuretic peptide (BNP) concentrations—1980 pg/mL and 2540 pg/mL, (laboratory normal values for adults <125 pg/mL) evaluated, respectively, on the 102nd and 153rd day of life (DOL), suggested right ventricle dysfunction, caused by increased resistance in pulmonary arteries.[9] Plasma BNP measurements were taken using the Elecsys proBNP II (Roche Diagnostics, Germany)

Therapeutic intervention

At the beginning of the sixth month of age (153 DOL), after obtaining parental approval, oral administration of supplement—L-citrulline (Nutricia Pure Amino Acid Powders; 100 g/tub) in a dose of 150 mg/kg/day was started. It was administered as a single dose a day. The infant was still receiving iNO and oral sildenafil. During the next 3 weeks, iNO had been gradually withdrawn and the infant was weaned from mechanical ventilation to noninvasive positive pressure ventilation (NIPPV). It is important to stress that the patient was never intubated again, until he was discharged. Within the next 15 days, NIPPV was superseded by nasal continuous positive airways pressure (n-CPAP). This type of noninvasive ventilatory support was continued for the next 4 weeks. L-citrulline was supplemented for a total period of 70 days and was discontinued together with oral sildenafil.

Timeline

Plasma BNP concentrations were decreasing continuously and after 1 month of L-citrulline administration they reached the values, closed to the normal limits for the age interval between 6 and 12 months of life (Figure 1).

There were no symptoms of L-citrulline intolerance observed during supplementation. Moreover, an evaluation of plasma L-citrulline concentration (tandem mass spectrometry) after 1 month of administration showed the value of 35 µmol/L, which was within the normal range for infants (6.6–41.3 µmol/L).[10] The sample of blood for plasma L-citrulline evaluation was obtained about 1 h before administration of supplement. At discharge, the patient required intermittently, exclusively during feeding, a supply of 22%–25% concentration of oxygen.

Discussion

Citrulline is a water-soluble, non-essential amino acid, synthesized in the liver and in the enterocytes, which are the major source of endogenously produced blood-borne L-citrulline. This amino acid is used as a replacement therapy for children with certain types of urea cycle defects. These children receive L-citrulline for decades and present no evidence of toxicity from its administration.[11]

This is the first report of the use of orally administered L-citrulline in infant with BPD, complicated with chronic PH. We initially decided to administer orally, a dose of L-citrulline: 150 mg/kg, which was given intravenously for the prevention of postoperative PH.[10] A total daily dose of L-citrulline

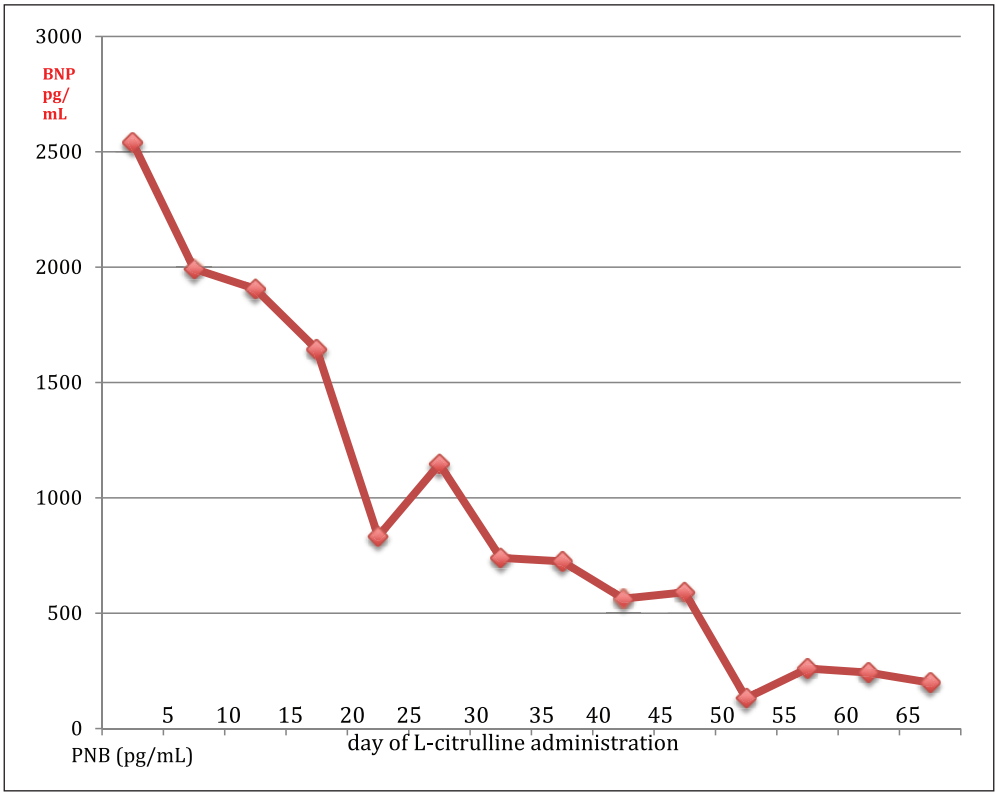

Figure 1. Plasma BNP concentrations evaluated during the oral administration of L-citrulline.

supplementation in our patient oscillated between 0.6 and 0.8 g of amino acid. It is important to stress that plasma L-citrulline concentration, evaluated after 1 month of oral administration, showed three times lower value when compared with those found after intravenous administration a dose of 150 mg/kg. However, our patient was a premature infant and the study that evaluated intravenous L-citrulline administration was performed in older children. We speculate that bioavailability of L-citrulline may be dependent on the functional maturity of the digestive tract of the individual patient and that the possible adjustments of doses should be made depending on the gestational or postnatal age.

Moreover, the range of "normal" L-citrulline concentrations is quite large, and although it did include 35 µmol/L, it was entirely possible that the infant's plasma L-citrulline concentrations were much lower prior to starting the supplement administration and that a value of 35 µmol/L, might reflect a significant increase.

After 6 weeks of L-citrulline administration, we obtained a normalization of plasma BNP concentration. To prolong a beneficial effect, we continued amino acid administration for the next 6 weeks with simultaneous evaluation of plasma BNP levels.

We decided to introduce L-citrulline into therapy as a noninvasive, relatively safe supplement, which gave the prospect for beneficial effects. However, we realize that 150 mg/kg/day is neither an optimal dose nor is the period of 70 days an optimal length of treatment with L-citrulline. Also, neither the pharmacokinetics of oral L-citrulline nor the target plasma concentration in infants is known. However, we speculate that calculation of the appropriate dose and the length of period of L-citrulline oral administration might be based on the values of plasma BNP concentrations, evaluated during amino acid supplementation.

Conclusion

Our preliminary results indicate that L-citrulline supplementation might be a potential therapy for chronic PH in infants with BPD. However, a large multicenter randomized clinical trial is required to confirm the potentially beneficial alternative in the prophylaxis or therapy of chronic PH in infants.

Acknowledgements

The authors have no commercial, proprietary, or financial interest in the products and companies described in this article. R.L. wrote the report and made substantial contributions to the conception and design of the manuscript. D.P. and J.P.L. critically revised the manuscript and were involved in drafting and revising the manuscript for important content. All the authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

The parental approval was obtained for oral administration of supplement—L-citrulline. Also, the parental informed consent was given for data publication. Written informed parental consent was obtained from the parents of infant for their anonymized information to be published in this article.

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