

## Letter to the Editor

# Comment on “New Antioxidant Drugs for Neonatal Brain Injury”

**Lajos Lakatos<sup>1</sup> and György Balla<sup>2,3</sup>**

<sup>1</sup>Department of Pediatrics, Kenezy Teaching Hospital, Bartók B. Street 2-26, Debrecen 4031, Hungary

<sup>2</sup>Hungarian Academy of Sciences, Hungary

<sup>3</sup>Department of Pediatrics, Faculty of Medicine, University of Debrecen, Nagyerdei Körút 98, Debrecen 4012, Hungary

Correspondence should be addressed to Lajos Lakatos; [lakatosl@kenezykorhaz.hu](mailto:lakatosl@kenezykorhaz.hu)

Received 10 July 2015; Accepted 20 August 2015

Academic Editor: Felipe Dal Pizzol

Copyright © 2015 L. Lakatos and G. Balla. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In their thought-provoking and well-documented review, Tataranno et al. [1] have summarized the “new body” of knowledge about antioxidant drugs for neonatal brain injury. The authors, however, did not mention that D-Penicillamine (DPA) therapy is being used in the neonatal period (treatment in various forms of hyperbilirubinemia [2] and the prevention of retinopathy of prematurity (ROP), which, despite its peripheral location, the retina or neural portion of the eye, is actually part of the central nervous system [3, 4]) ever since 1973. Our recently published case reports, together with other convincing cases which participated in the long-term (28–40 years) follow-up, suggested that DPA therapy of newborn infants may have significant neuroprotective effects in cases jeopardized by bilirubin-induced neurologic dysfunction (BIND) or ROP [5]. This unexpected effect may be related to DPA capability to alter the nitric oxide (NO) system [6–9] and its strong antioxidant effects [10–12]. NO synthesized in the central nervous system produces a myriad of effects. For example, it plays a role in the control of blood flow, learning and memory, neurotransmitter release, gene expression, immune responsiveness, and cell survival. It is also implicated in numerous pathologies such as Alzheimer's disease, Huntington's disease, cerebral ischemia, and disorders of the basal ganglia caused by metals (Wilson's disease), bilirubin (BIND), or other pathologic conditions (Parkinsonism). The use of chelation therapy for nonmetal overload indications continues to be investigated. Furthermore, the mechanism of DPA in the reduction of serum bilirubin is

based on the fact that this drug inhibits the rate limited enzyme (heme oxygenase) in heme metabolism [13]. Because those enzymes that play an important role in antioxidant defense and drug metabolism (peroxidases, catalase, and cytochrome P-450) are heme proteins, it can be assumed that in preventing hyperbilirubinemia, ROP, and oxygen toxicity, the mechanism of action of DPA is identical: the protection of biomembranes against lipid peroxidation caused by free radical. Low molecular weight disulfides are the major products of DPA metabolism in humans. The oxidation of DPA in vivo may also important in the mode of action of the drug through simultaneous reduction of oxygen species. Finally, we can say that DPA fulfills the criteria of a hybrid drug in the neonatal period by its ability to modulate both oxidative stress and NO pathway and can be a neuroprotective agent in the pathophysiology of neurologic dysfunction [14].

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## References

- [1] M. L. Tataranno, S. Perrone, M. Longini, and G. Buonocore, “New antioxidant drugs for neonatal brain injury,” *Oxidative Medicine and Cellular Longevity*, vol. 2015, Article ID 108251, 13 pages, 2015.

- [2] L. Lakatos, "Bloodless treatment of infants with Haemolytic disease," *Archives of Disease in Childhood*, vol. 89, no. 11, article 1076, 2004.
- [3] D. L. Phelps, L. Lakatos, and J. L. Watts, "D-penicillamine for preventing retinopathy of prematurity in preterm infants," *Cochrane Database of Systematic Reviews*, no. 1, Article ID CD001073, 2001.
- [4] D. Purves, *Neuroscience*, Sinauer Associates, Sunderland, Mass, USA, 2nd edition, 2001.
- [5] L. Lakatos, G. Balla, I. Pataki, Z. Vekerd-Nagy, and G. Oroszlán, "D-penicillamine in the neonatal period: case reports," *International Journal of Medical and Pharmaceutical Case Reports*, vol. 4, no. 3, pp. 59–63, 2015.
- [6] S. H. Snyder, "Nitric oxide: first in a new class of neurotransmitters," *Science*, vol. 257, no. 5069, pp. 494–496, 1992.
- [7] L. Lakatos and G. Oroszlán, "Possible effect of D-penicillamine on the physiologic action of inhaled nitric oxide in neonates," *Journal of Pediatrics*, vol. 124, no. 4, pp. 656–657, 1994.
- [8] M. Feelisch, "The use of nitric oxide donors in pharmacological studies," *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 358, no. 1, pp. 113–122, 1998.
- [9] S. M. March, P. Abate, N. E. Spear, and J. C. Molina, "The role of acetaldehyde in ethanol reinforcement assessed by Pavlovian conditioning in newborn rats," *Psychopharmacology*, vol. 226, no. 3, pp. 491–499, 2013.
- [10] D. A. Joyce and R. O. Day, "D-penicillamine and D-penicillamine-protein disulphide in plasma and synovial fluid of patients with rheumatoid arthritis," *British Journal of Clinical Pharmacology*, vol. 30, no. 4, pp. 511–517, 1990.
- [11] O. D. Saugstad, "Oxygen toxicity in the neonatal period," *Acta Paediatrica Scandinavica*, vol. 79, no. 10, pp. 881–892, 1990.
- [12] J. Sanderud, G. Oroszlán, K. Bjoro, M. Kumlin, and O. D. Saugstad, "D-penicillamine inhibits the action of reactive oxygen species in the pig pulmonary circulation," *Journal of Perinatal Medicine*, vol. 23, no. 5, pp. 385–393, 1995.
- [13] G. Oroszlán, L. Lakatos, L. Szabó, B. Matkovics, and L. Karmazsin, "Heme oxygenase activity is decreased by D-penicillamine in neonates," *Experientia*, vol. 39, no. 8, pp. 888–889, 1983.
- [14] M. Godínez-Rubí, A. E. Rojas-Mayorquín, and D. Ortuño-Sahagún, "Nitric oxide donors as neuroprotective agents after an ischemic stroke-related inflammatory reaction," *Oxidative Medicine and Cellular Longevity*, vol. 2013, Article ID 297357, 16 pages, 2013.

