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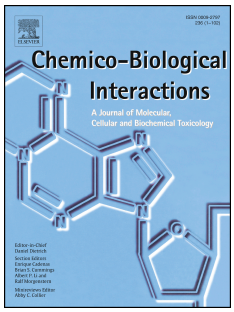

Penicillamine - not only a chelating agent but also a potent neuroprotector in the neonatal period

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A letter to The Editor

Chemico-Biological Interactions journal

Penicillamine - not only a chelating agent but also a potent neuroprotector in the neonatal period

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We read with interest the article written by Božić *et al* [1]. More than 6 decades ago the aminoacid dimethylcysteine (penicillamine) was introduced into clinical medicine as a chelating agent [2] and the time is now ripe to review what is known of the chemistry, pharmacology and therapeutic action of this compound. D-penicillamine (D-PA) was first recognized as a potential benefit for neonatal hyperbilirubinemia. During this time there was a remarkably low incidence of retinopathy of prematurity in the infants treated with D-PA [3]. Later, our studies were replicated in other institutes in Hungary, Poland, U.S. A., India and Mexico [4-15]. It is important to note that there was no intolerance or short- or long-term toxicity of the medication, in spite of the fact that in the newborn period D-PA was used 10-20 times higher doses than those in adult. Furthermore, the aim of our recent article [16] was to demonstrate a new concept in the etiology of bilirubin-induced neurologic dysfunction (BIND) and highlight the role of D-PA. Unconjugated bilirubin has a special affinity for the globus pallidus, the hippocampus, and the subthalamic nucleus (basal ganglia). The copper metabolism in Wilson's disease and in newborn infants is strikingly similar. Both have large quantities of copper in the liver which is contrasted by an unusually low ceruloplasmin level in the blood. In strictly biological terms, at least 3 loci exist where UCB and copper can be "fusioned" in the neonatal period: (1) during hemolysis high UCB

and copper level can be developed in the blood; (2) one albumin can bind one Cu++ in the primary binding site. At higher concentration of copper (if possible under certain conditions), loosely bound atoms, and can be very easily taken out by UCB. The bile pigment itself can displace loosely bound copper ions, which are electrostatically attached due to high negative charge on the surface of albumin; (3) in the basal ganglia. Beside copper mobilization D-PA may play an important role in maintaining the sulphhydryl-disulphide equilibrium, thus, stabilizing the oxidation-reduction potential in the cell [17]. We hope that our concept will help answer the unsolved questions and concerns ocurred in the etiology and pathomechanisms of BIND and other neurodegenerative/neurodevelopmental disorders (NDs). The beneficial neuropharmacological actions of metal-targeted (chelating) agents most likely arise from local metal redistribution rather than from massive metal removal. The chelation therapy for non-metal overload indications continues to be investigated. Our present letter address the medical necessity of the use of a chelating agent (D-PA) in the prevention or treatment of neonatal brain injuries [18]. In addition copper dyshomeostasis and oxidative stress have also been concerned in NDs such as autism spectrum disorder (ASD) [19,20].

References

1. B. Božić, J. Korać, D.M. Stanković, M. Stanić, A. Popović-Bijelić, J. Bogdanović Pristov, I. Spasojević, M. Bajčetić, Mechanisms of redox interactions of bilirubin with copper and the effects of penicillamine, Chemico-Biological Interactions (2017), doi: 10.1016/j.cbi.2017.10.022
2. Walshe JM. Treatment of Wilson's disease with penicillamine. Lancet 1 (1960) 188-92. doi:10.1016/S0140-6736(60)90109-4
3. Lakatos L, Hatvani I, Oroszlán G, Vekerdy Z, Alaka B, Kincses É. Controlled trial of D-Penicillamine to prevent retinopathy of prematurity. Acta Paediatr Acad Sci Hung 27(1986) 47-56.
4. Silverman WA. Where's the evidence? Debates in modern medicine. Oxford University Press 1998; Chapter 37. pp. 163-166
5. Dolinay T, Szombathy G. D-Penicillamin felhasználása az újszülöttkori hyperbilirubinaemiák terápiájában. Orv Hetil 115 (1974) 1431-1432.
6. Korányi Gy, Kovács J, Vörös I. D-Penicillamine treatment of hyperbilirubinemias of preterm infants. Acta Paediatr Acad Sci Hung 19 (1978) 9-14.

7. Szűts A, Lechner E. ABO haemolytikus betegség konzervatív kezelése. Gyermekgyógyászat 50 (1999) 67-69.

8 Nagy A, Felszeghi E. Per os D-Penicillaminnal és fototerápiával sikeresen kezelt Rh-isoimmunisation. Gyermekgyógyászat 51 (2000) 81-83.

9 Rokicki, W. D-Penicylamina-nowy lek w profilaktyce I terapii noworodka? D-Penicillamine - A New Drug For Prevention And Treatment In Neonates. Polish - Przeg Ped 19 (1989) 229-233.

10. Aldana-Valenzuela C. Personal information during a lecture-tour in Mexico (2008).

11. Lakatos L, Phelps DL, Watts JL. International replications, anyone? Arch Dis Child Fetal Neonatal Ed 80 (1999) F252.

12. Christensen RD, Alder SC, Richards SC et al. D-Penicillamine administration and incidence of retinopathy of prematurity. J Perinatol 27 (2007) 103-111.

13. Tandon M, Dutta S, Dogra MR et al. Oral D-penicillamine for the prevention in very low birth weight infants: a randomized, placebo-controlled trial. Acta Paediatr 99 (2010) 1324-1328.

14. Phelps DL, Lakatos L, Watts, JL. D-Penicillamine for preventing retinopathy of Prematurity. Cochrane Database Syst Rev (1): CD001073 (2001).

15. Qureshi MJ, Kumar M. D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Cochrane Database Syst Rev 3 (2013) 9: CD001073.

16. Lakatos L., Balla G. Bilirubin-induced neurologic dysfunction (BIND): appearances are fairly often deceptive. Birth Defects 1 (2017) 1-4. doi: 10.15761/BDJ.1000109

17. Rupp H., Weser U. Reactions of D-penicillamine with copper in Wilson's disease. Biochem Biophys Res Com 72 (1976) 223-229.

18. Lakatos L, Balla G, Pataki I. Copper-induced oxidative/nitrosative stress and excitoxicity in the neonatal period: neuroprotection with D-Penicillamine. Ped Dimens 2 (2017) 1-6. doi: 10.15761/PD.1000143

19. Lakatos L, Pataki I., Balla G., Vekerdy-Nagy Z. Penicillamine - Preventing or “Curing” Autism Spectrum Disorders in the Neonatal Period?”. EC Paediatrics 6 (2017) 51-52.

20. Lakatos L, Balla G, Pataki I, Vekerdy-Nagy Z. Penicillamine-from the BIND, through the ROP, till the ASD in the Neonatal Period.
EC Neurology SI. 01 (2017) 14-17.