InnoVationinfo

Journal of Pediatrics and Infants

ISSN: 2581-7493
Volume 2: 1
J Pediat Infants 2019

Penicillamine in the Neonatal Period: The Intravenous Administration is More Effective than the Oral Route as a Chelating Agent, Antioxidant and Neuroprotector; But the Iv Preparation is Not Available

Lajos Lakatos*

Neonatologists in the world, Food and Drug Administration (FDA), Biological and Pharmaceutical Scientists and Factories, Hungary

Abstract

Introduction: Heavy metal ions, especially copper and iron play very important roles in the pathogenesis of neurodevelopmental and neurodegenerative diseases including Bilirubin-Induced Neurologic Dysfuction (BIND), Retinopathy Of Prematurity (ROP) and - may be - Autism Spectrum Disorder (ASD). In addition, the copper metabolism in Wilson's disease and in newborn infants is strikingly similar. Both have large quantities of copper in the liver and brain which is contrasted by an unusually low ceruloplasmin level in the blood.

Purpose: It is a „new" drug approval for 2019: D-penicillamine (D-PA) which can administer intravenously. The most effective IV preparation of this orphan drug now is not available in the drug market.

Methods: The author analyzed the literature and incorporated the own clinical experiences which are more than 40 years. In the mean time, our studies were replicated in other institutes in Hungary, Poland, the US, India and Mexico. 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 D-PA was used 10-20 times higher doses in the newborn period, than those in adult.

Conclusion: To the new concept, the BIND, ROP and ASD are neurodegenerative and neurodevelopmental diseases (NDs) of immature brain caused by accumulation of free metals, Unconjugated Bilirubin (UCB), and UCB-Cu complex (as prooxidant), respectively, in the Basal Ganglia (BG) and other parts of the Central Nervous System (CNS). The main factor is the hemolysis of neonatal red blood cells. This process is going with the induction of a great amount of heavy metals (mainly copper and iron) and producing reactive oxygen species (ROS). These elements are circulating in the bloodstream, and pass through the immature blood-brain-barrier (BBB), finding entrance into the CNS. In addition, ROS contribute to increased BBB permeability creating a dangerous vitious circle in the neonatal brain. The intravenously administered D-PA would be effective to prevent of these processes.

Keywords: D-Penicillamine in the Neonatal Period; Orphan Drug; Copper Hypothesis of BIND, ROP and ASD; Follow-Up Studies.

Abbrevations

ASD: Autistism Spectrum Disorder; BG: Basal Ganglia; BIND: Bilirubin-Induced Neurologic Dysfunction; BBB: Blood-Brain-Barrier; CNS: Central Nervous System; Cp: Ceruloplasmin; D-PA: D-Penicillamine; ET: ExchangeTransfusion; IV: Intravenously; ND: Neurodegenerative or Neurodevelopmental Disease; ROP: Retinopathy of Prematurity; ROS: Reactive Oxygen Species; VLBW: Very Low Birth Weight

Article Information

Article Type: Research

Article Number: JPI118

Received Date: 25 June, 2019

Accepted Date: 01 August, 2019

Published Date: 06 August, 2019

***Corresponding author:** Lajos Lakatos MD, DSc, Neonatologists in the world, Food and Drug Administration (FDA), Biological and Pharmaceutical Scientists and Factories, Hungary. Tel: (+36 52) 411-600/56288; Email: lakatosl(at)kenezykorhaz.hu

Citation: Lakatos L (2019) Penicillamine in the Neonatal Period: The Intravenous Administration is More Effective than the Oral Route as a Chelating Agent, Antioxidant and Neuroprotector; But the Iv Preparation is Not Available. J Pediat Infants Vol: 2, Issu: 1 (24-27).

Copyright: © 2019 Lakatos L. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

A recent report by the National Research Council found that „50% of all pregnancies in the US are now resulting in prenatal or postnatal mortality, significant birth defects, developmental neurological problems, or otherwise chronically unhealthy babies. The incidence of neurotoxic or immune reactive conditions such as autism, schizophrenia, Attention Deficit Disorder (ADD), dyslexia and learning disabilities have been increasing rapidly in recent years" [1]. In the body, misplaced iron and copper ions serve as catalysts to initiate and accelerate oxygen radical activity. The interaction between an oxygen radical and its target produces a cascade of free radicals. Left unchecked, they will in turn attack and disrupt nearby cells that will also produce torrents of additional free radicals, and also so on [2,3].

So how do we protect ourselves against the objectionable oxygen radicals? Fortunately, cells contain built-in safeguards highly effective enzyme systems that produce Superoxide Dysmutase (SOD), catalase, and glutathione peroxidase. Serving as a back-up crew are anti-oxidants such as vitamins E and C, beta-carotene, and glutathione [4], and *penicillamine* [5] which structurally similar to the latter molecule [6] .

Free radicals and related reactive species are drawning towards copper and iron ions [7]. They attack cells in the vicinity, disrupting cell membranes, enzymes systems, neurotransmitters, and neuroreceptors. Neuro-systems are particularly susceptible to peroxidative destruction because of their high concentration of fat insulation.

D-PA can maintain cellular health by reducing free radical pathology by removing the metal ions (especially copper and iron) that are the catalists for lipid peroxidation [8].

Chelation with D-PA? It must be something new

There is always the possibility, of course, that neonatologists who have snubbed D-PA chelation just don't know any better. Even if doctors were to read this therapy, many probably would not understand it. All too often, rejection is based on the fear a new therapy would out-date their skills and result in lost patients, lost revenue and professional obsolescence. The chance for mega-profits is just as upt to decide which treatments are featured and marketed by the medical monopoly as in any competitive arena [9].

The benefits of D-PA therapy opposite the exchange transfusion (ET)

The ET is hazardous, expensive, and requires extensive hospitalitation; the D-PA is relatively inexpensive, pain free, safe, effective and convenient. The ET, like a surgery intervention, is traumatic, disruptive, and requires a prolonged hospital stay; chelation is easily available (unfortunately, now only the per os preparation) - no stress, no fuss, no complicated preparation like before ET [10].

Has it been tested or proven already?

This is a monotonous oft-repeated criticism agains D-PA treatment. Although a number of qualified physicians have practiced chelation in the neonatal period safely and effectively in Hungary, Poland, the US, India [11,12,13,14, 15,16,17,18,19,20,21] and other foreign countries *during the last forty years*, traditional medicine continues to refuse it. When sufficient time has elapsed to fully evidence its importance, someone can say: Yes, surely it is important, but it is no longer new.

Intravenous administration of D-PA is more beneficial in the neonatal period than oral route

Generally, which has been written in Table 1. is also valid for the intravenous treatment in the neonatal period. However, in the case of oral D-PA therapy the absorption is too slow, and the plasma concentration is very low [23]; opposite the intravenous route, which insures a high blood level promptly [24,25]. Since it has been declared by FDA that it is an orphan drug [26] the intravenous D-PA is not available in the drug market. „An orphan drug is a pharmaceutical agent developed to treat medical conditions which, because they are so rare, would not be profitable to produce without government assistance. The conditions are referred to as orphan diseases". Question: are neonatal disorders - BIND, ROP, ASD, ADD et cet. - rare i.e. orphan diseases??

Chowrimooto et al. more than 20 years ago [26] pointed out that: "fetal copper metabolism is different from that of the adult,...with apparent similarity to Wilson's disease." Fetal copper metabolism is different from that of the adult [27,28] with the fetal liver tolerating up to 20 times the adult liver copper concentration without damage. This apparent similarity to Wilson's disease has led to the suggestion that in this disease there is a failure to change from the neonatal mode of copper metabolism to the adult mechanism. [30,31]. In both Wilson's disease and the normal fetus biliary copper excretion is greatly reduced, with low plasma copper and absent or low plasma caeruloplasmin concentrations.

Conclusion

Heavy metal ions, especially copper and iron play a pivotal role in the pathogenesis of neurodegenerative diseases including BIND, having impact on both protein structure (misfolding) and oxidative stress. Our recently

Table 1: Pros and cons of intravenous administration of a drug [22]

Intravenous
Pros
• Dependable and reproducible effects
• Entire administered dose reaches the systemic circulation immediately – the dose can be accurately titrated against response
Cons
• Requires a functioning cannula
• More expensive and labour intensive than other routes.
• Cannulation is distressing to some patients, especially children
• Cannulae are prone to infection
• IV injection of drugs may cause local reactions

published case report and other healthy and highly educated patients' (they are now 28 to 42 years old) follow-up suggest that D-PA administration to the newborn infants may have significant neuroprotective effects in cases jeopardized by BIND or ROP. In addition, it was our privilege to follow a number of children who are now adults, including sons and daughters of our relatives, colleagues and close friends. They are now highly educated persons working in health care (mostly as physicians), bank, computer, and building industry, etc. Copper dyshomeostasis and oxidative stress have also been concerned in neurodegenerative/ neurodevelopmental disorders such as ASD or ADD [32]. Our recommendation: all newborns should be screened for ASD, particularly the premature babies (especially the very low birthweight infants -VLBW) and infants suffering from NHBI. These conditions significantly increase the prevalence of NDs, including ASD and ADD. Although the 24 hour urine copper test is inconsistent in the neonatal period, the Penicillamine challenge test may be useful in the detection of higher copper in the urine. For those children who are voiding copper more than usually in the given institutes or laboratories, high doses D-PA therapy is necessary for 2 to 3 weeks. Our concept was conceived because of long-term follow up (3 to 40 years) we found only 1 ASD in the children and adults who were treated with D-PA in their neonatal period (N=550 patients so far; - According to the Johns Hopkins University Bloomberg School of Public Health U.S. autism rate up 15 percent over two-year period [33,34,35,36,37,38,39]). The intravenously administered D-PA would be effective to prevent of these processes.

References

1. Boyle MM, Beaty G (2010) How Heavy Metals Affect Neurotransmitters Production and Balance.
2. Perrone S, Tataranno ML, Stazzoni G, Buonocore G (2012) Oxidative stress and free radicals related diseases of the newborn. Adv Biosci Biotechn 3: 1043-1050.
3. Martinez A, Reina M (2017) .Copper or free radical scavenger? Computat Theoret Chem 1104: 1-11.
4. Sanjeev K (2017) How do we prevent free radicals from damaging us forever?
5. Leung BO, Jalilehvand F, Mah V, Parvez M, Wu Q (2013) Silver(I) Complex formation with Cysteine, Penicillamine and Glutathione. Inorg Chem 2: 4593-4602.
6. Miki M (1994) Penicillamine as antioxidant. Methods in Enzymology 234: 542-547.
7. Jomova K, Valko M (2011) Advances in metal-induced oxidative stress and human disease. Toxicology 283: 65-87.
8. Ayala A, Munoz MF, Argüelles S (2014) Lipid Peroxidation: Production, Metabolism, and Signaling Mechanisms of Malondialdehyde and 4-Hydroxy-2-Nonenal. Oxid Med Cell Long 2014: 360438.
9. Siddiqui G (2018) Why Doctors Reject Tools That Make Their Jobs Easier?
10. Evans N (2011) Neonatal exchange transfusion.
11. Lakatos L, Kover B, Péter F (1974) D-Penicillamine Therapy In The Neonatal Hyperbilirubinaemias. Acta Paediatr Acad Sci Hung. 15: 77-85.
12. Lakatos L, Kover B, Oroszlan G, Vekerdy Z (1976) D-Penicillamine Therapy in AB0 Hemolytic Disease of the Newborn Infant. Europ J Pediat 123:133-137.
13. Korányi G, Kovács J, Vörös I (1978) D-Penicillamine treatment of hyperbilirubinemias of preterm infants. Acta Paediatr Acad Sci Hung 19: 9-16.
14. Szuts A, Lechner E (199) ABO haemolytikus betegség konzervatív kezelése. Gyermekgyógyászat 50: 67-69.
15. Nagy A, Felszeghi E (2000) Per os D-Penicillaminnal és fototerápiával sikeresen kezelt Rh-isoimmunisation. Gyermekgyógyászat 51: 81-83.
16. Rokicki W (1989) D-Penicylamina-nowy lek w profilaktyce I terapii noworodka? (D-Penicillamine -A New Drug for Prevention And Treatment In Neonates. Polish -Przeg Ped 19: 229-233.
17. Christensen RD, Alder SC, Richards SC, Lambert DK, Schmutz N, et al. (2007) D-Penicillamine administration and the incidence of retinopathy of prematurity. J Perinatol 27: 103-111.
18. Tandon M, Dutta S, Dogra MR, Gupta A (2010) Oral D-penicillamine for theprevention of retinopathy of prematurity in very low birth weight infants: a randomised, placebo-controlled trial. Acta Paediatrica 99: 1324-1328.
19. Phelps DL, Lakatos L, Watts JL (2001) D-Penicillamine for preventing retinopathy of Prematurity. Cochrane Database Syst Rev: CD001073
20. Qureshi MJ, Kumar M (2013) D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Cochrane Database Syst Rev: CD001073.
21. Valenzuela CA (2008) Personal communication in Mexico during a lecture-tour.
22. Pros and cons of different routes of drug administration.
23. Christensen RD (2007) Personal communication.
24. Oroszlan G, Szabó T, Lakatos L (1987) The pharmacokinetics of D-penicillamine in neonates. Acta Paediatr Hung 28: 143-146.
25. Linakis MW, Roberts JK, Lala AC, Spigarelli MG, Medlicott NJ, et al. (2016) Chellenenges Associated with Route of Administration in Neonatal Drug Delivery. Clin Pharmacokinet 55: 185-196.
26. Orphan drug. From Wikipedia, the free encyclopedia. https://en.wikipedia.org/wiki/Orphan_drug
27. Chowrimootoo G, Scowcroft H, Seymour C (1998) Caeruloplasmin isoforms in Wilson's disease in neonates. Arch Dis Child Fetal Neonatal Ed 79: F198-F201.
28. Gutteridge JMC, Stocks J (1981) Caeruloplasmin: physiological and pathological perspectives. Crit Rev Clin Lab Sci 14: 257-329.
29. Aggett PJ*(1994)* Aspects of neonatal metabolism of trace metals. Acta Paediatr Suppl 402: 75-82.
30. Epstein O, Sherlock S (1981) Is Wilson's disease caused by a controller gene mutation resulting in the perpetuation of the foetal mode of copper metabolism into childhood? Lancet 317: 303-305.
31. Srai SK, Burroughs AK, Wood B, Epstein O (1986) The ontogeny of liver copper metabolism in the guinea pig: clues to the etiology of Wilson's disease. Hepatology 6: 427-432.
32. Gale C, Statnikov Y, Jawad S, Uthaya SN, Modi N (2018) Neonatal brain injuries in England: Population-based incidence derived from routinely recorded clinical data held in the National Neonatal Research Database. Arch Dis Child Fetal Neonatal Ed 103: F301-F 306.
33. Balla G, Lakatos L (2015) D-Penicillamine as a neonatal neuroprotectant: Clinical and neurodevelopmental studies. Int J Cur Res. 7: 21282-6.
34. Johns Hopkins University Bloomberg School of Public Health. (2018) U.S. autism rate up 15 percent over two-year period.
35. Lakatos L, Pataki I, Balla G, Nagy ZV (2018) Potential Role of penicillamine in the early diagnosis and prevention of autism spectrum disorder (ASD). SF J Autism 2: 1-12.
36. Lakatos L, Balla G, Pataki I, Vekerdy Z (2017) Penicillamine-from the BIND, through the ROP, till the ASD in the Neonatal Period. EC Neurology SI 01: 14-17

37. Lakatos L, Balla G, Pataki I, Vekerdy Z (2017) Penicillamine - Preventing or "Curing" Autism Spectrum Disorders in the Neonatal Period?". EC Paediatrics 62: 51-52.

38. Lakatos L (2018) D-Penicillamine in the Neonatal Period: Past (!), Present (!?) and Future (?!). Int J Pediatr Res 4: 47-53.

39. Lakatos L (2018) Early Diagnosis and Prevention of Hyperbilirubinemia and Autism Spectrum Disorder. Clin Res Pediatr 1: 1-2.

Citation: Lakatos L (2019) Penicillamine in the Neonatal Period: The Intravenous Administration is More Effective than the Oral Route as a Chelating Agent, Antioxidant and Neuroprotector; But the Iv Preparation is Not Available. J Pediat Infants Vol: 2, Issu: 1 (24-27).