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Penicillamine-from the BIND, through the ROP, till the ASD in the Neonatal Period

Mini Review

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Abstract

D-penicillamine (D-PA) was first recognized as a potential benefit for neonatal hyperbilirubinemia (NHBI) caused by hemolytic diseases of the newborn infant or immaturity of UDP-glucuronyltransferase enzyme. During this time there was a remarkedly low incidence of retinopathy of prematurity (ROP) in the infants treated with D-PA. Later, our studies were replicated in other institutes in Hungary, Poland, USA, 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 DPA was used 10-20 times higher doses in the newborn period, than those in adult age. To our concept, the bilirubin-induced neurologic dysfunction (BIND), ROP and Autism Spectrum Disorders (ASD) are neurodegenerative and neurodevelopment diseases (NDs) of immature brain caused by accumulation of free metals and unconjugated bilirubin (UCB), and UCB-Cu complex (as prooxidant), respectively, in the basal ganglia (BG) and other parts of the central nervous system (CNS) relevant to the above mentioned conditions. 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 iron and copper) 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.

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

Abbrevations

ASD: Autistism Spectrum Disorders; BG: Basal Ganglia; BIND: Bilirubin-Induced Neurologic Dysfunction; BBB: Blood-Brain-Barrier: CNS: Central Nervous System; Cp: Ceruloplasmin; D-PA: D-Penicillamine; ET-1: Endozhelin-1; HO: Heme Oxygenase; iNOS: Inducible Nitric oxide Synthase; MD - Metal Dyshomeostasis; NHBI: Neonatal Hyperbilirubinemia; ND: Neurodegenerative or Neurodevelopmental Disease; OS/NS: Oxidative/Nitrosative Stress; ROP: Retinopathy of Prematurity; ROS: Reactive Oxygen Species; UCB: Unconjugated Bilirubin; VEGF: Vascular Endothelial Growth Factor; WD: Wilson's Disease

Introduction

When in the early 1970s, we reviewed the role of D-PA in the treatment of NHBI, the drug was new to most neonatologists [1,2]. The idea that D-PA might be a suitable drug to act as a copper-binding agent for use to control icterus neonatorum occurred, serendipituously, to one of us (L.L) while reflecting on the similarity of copper storage in Wilson's disease (WD) and neonates. It is well known that all neonates have increased concentration of copper in their liver and brain, and a decreased concentration of a specific plasma copper-protein, ceruloplasmine (Cp), in comparison with individuals over one year old [3].

D-PA in NHBI

D-PA, given intravenously to newborns, greatly reduces the plasma bilirubin concentration or prevents its increase, which is usually seen during the first few days of life. This treatment is especially effective in jaundice of hemolytic origin, such as AB0- or Rhesus-incompatibility, and is used together with phototherapy in several neonatal units in Hungary where it has largely replaced exchange transfusions [4]. To our concept, the BIND is a neurodegenerative disease (ND) of immature brain caused by accumulation of free metals and UCB, and UCB-Cu complex (as prooxidant), respectively, in the basal ganglia (BG) and other parts of the CNS relevant to BIND. The main factor is the hemolysis of neonatal red blood cells. This process is going with the induce of a great amount of heavy metals (mainly iron and copper) and producing reactive oxygen species (ROS). They 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, especially in the BG [5]. More recently, our concept was confirmed by Božić B. *et al.* [6] with convincing chemistry experiments. Fortunately, the developmental pharmacology and the age related effects of D-PA largely favoured by the administration of unusually high dosis of this drug. Since heme metabolism is a crucial stage in UCB production, we examined the activity of heme oxygenase (HO), the initial and rate-limiting enzyme of heme degradation. The 3 days of D-PA treatment in the adult animals did not lead to any significant change in HO activity. In contrast, *in neonates a marked reduction in enzyme activity was observed following DPA treatment* [7]. Other beneficial effects of D-PA in the neonatal period are as follows: *neuroprotection against copper-induced oxidative/nitrosative stress (OS/NS) and excitoxicity* [8]. Bizarrely, although it is a low-cost drug, at the same time developed under the Orphan Drug Act of 1983 in the US which is a federal law concerning rare diseases (orphan diseses) [9]. This means that pharmaceutical companies produce this "homeless, not a money-maker" drug with reluctance. For example, the intravenous form of D-PA is nowdays not available in the market and the per os preparation is produced by a few companies in the world.

Prevention of ROP with D-PA (clinical observations and prospective randomized conrolled trials)

Improved survival of low birth weight, premature babies in developing countries has increased the incidence of ROP [10]. According to a World Health Organization report [11] ROP is emerging as a maior cause of blindness in childhood. The disease prevention seems to be especially important because the therapy of ROP cases with cryotherapy or current methods of treatment rely on invasive laser procedures [12] that themselves lead to some vision loss. The biggest drawback of anti-VEGF (vascular endothelial growth factor) treatment with intravitreal Bevacizumab/Avastin® is exposing an immature infant to a drug for which experts cannot evaluate the systemic risk. For example, these infants with ROP are already prone to bronchopulmonary dysplasia, and the most significant target organs for damage from VEGF suppression are the alveoli [13]. The history of D-PA therapy in neonates under 1500 g birth weight can be divided into four periods [14], ending with the conduction of two strictly controlled, randomized; prospective trial to investigate its presumably beneficial effects not only in the prevention of the cicatricial form of the disease but also in the reduction of the acute stages [15,16]. Summarizing the results of these clinical trials: (1) D-PA treatment was associated with elimination of all stages of ROP. (2) In this single-centered comparison analysis, a 14-day course of D-PA administration resulted in no apparent short- and long-term toxicity. This drug may be regarded as causal agent in the prevention of ROP:

- By its antioxidant effects;
- By donating nitric oxide (NO) or
- By inhibiting inducible nitric oxide synthase (iNOS), endothelin-1 (ET-1), VEGF, and HO;
- It chelates and excreates copper and
- Has a low-molecular weight, active in CNS [5].

D-PA - how to prevent ASD in the Neonatal Period?

There is indeed an increased incidence of ASD worldwide. "New Prevalence Numbers for 2014: 1 in 45 US Children have autism" [17], and it is most common among boys. Copper is implicated directly or indirectly in the pathogenesis of a large number of neurological

diseases, including ASD [18], and we have found a direct evidence for the copper excess in the etiology of this disorder characterized by impairments in social interactions, communication, and emotional abilities, while sparing basic cognitive skills. It was recommended by us [19], that all newborns should be screened for ASD, particularly the premature babies and infants suffering from hyperbilirubinemia. These conditions significantly increases the prevalence of NDs, including ASD. Although the 24-hour urine copper test is inconsistent in the neonatal period, and the normal value range may vary among different laboratories, the *penicillamine challenge test* [20], has proved itself to be useful in the detection of high copper in the urine

Our concept was conceived because of long-term follow-up (3 - 40 years [21]) 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). The 30 years old male patient was born as a premature infant and had a serious hyperbilirubinemia. He was treated with D-PA without success, because exchange transfusion was necessary.

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