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NEUROPROTECTIVE EFFECTS OF D - PENICILLAMINE IN THE NEONATAL PERIOD

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Abstract

Originally D-penicillamine (D-PA) was used due to its potential benefits in the treatment of neonatal hyperbilirubinemia caused by hemolytic diseases in newborn infants or immaturity of the liver enzyme uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase). In that period, the prevalence of retinopathy of prematurity (ROP) in infants who received treatment with D-PA. Later, studies were performed by different institutes in Poland, Hungary, the USA, Mexico, and India. Short or long-term use of the medication didn't seem to have caused toxicity or intolerance, even D-PA in the newborn period was given in higher doses compared with the doses used in adult patients. Several bilirubin-induced neurologic dysfunctions in the infants, including ROP and autism spectrum disorder, are possibly caused by metal accumulation, unconjugated bilirubin (UCB), as well as UCB-copper complexes in sensitive regions of the central nervous system. Apparently, neonatal hemolysis of red blood cells leads to an unphysiological release of copper and iron from the cells, which pass the blood-brain-barrier (BBB) via the bloodstream. Also, reactive oxygen species contributing to an increased BBB permeability, which creates a dangerous vicious circle in the neonatal brain. In this paper, we present two cases of neonatal hyperbilirubinemia, which indicate the potential neuroprotective effects of D-PA.

Key words: *D-penicillamine; copper; bilirubin; neurologic dysfunction; retinopathy prematurity; autism.*

Резюме

НЕЙРОПРОТЕКТОРНЫЕ ЭФФЕКТЫ Д - ПЕНИЦИЛЛАМИНА В НЕОНАТАЛЬНОМ ПЕРИОДЕ

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D-пеницилламин (D-PA) изначально нашел применение благодаря его потенциальным преимуществам в лечении гипербилирубинемии новорожденных, вызванной гемолитическими заболеваниями или незрелостью фермента печени уридин-5'-дифосфо-глюкуронозилтрансферазы (UDP-глюкуронозилтрансферазы). В тот период была установлена повышенная распространенность ретинопатии недоношенных (ROP) у детей, получавших лечение D-PA. Позднее исследования проводились различными институтами в Польше, Венгрии, США, Мексике и Индии. Кратковременное или длительное использование препарата, по-видимому, не вызывало токсичности или непереносимости, D-PA в период новорожденности даже давали в более высоких дозах по сравнению с дозами, применяемыми у взрослых пациентов. Некоторые вызванные билирубином неврологические дисфункции у детей, включая ROP и расстройства аутистического спектра, возможно, вызваны накоплением металлов, неконъюгированным билирубином (UCB), а также UCB комплексами с медью в чувствительных областях центральной нервной системы. По-видимому, неонатальный гемолиз эритроцитов приводит к нефизиологическому выделению меди и железа из клеток, которые проходят через гематоэнцефалический барьер (ГЭБ) через кровоток. Кроме того, активные формы кислорода способствуют увеличению проницаемости ГЭБ, что создает опасный порочный круг в мозге новорожденных. В этой статье мы представляем два случая гипербилирубинемии новорожденных, которые указывают на потенциальные нейропротективные эффекты D-PA.

Ключевые слова: *D-пеницилламин; медь; биллирубин; неврологическая дисфункция; ретинопатия новорожденных; аутизм.*

Түйіндеме

НЕОНАТАЛДЫ КЕЗЕҢДЕГІ Д-ПЕНИЦИЛЛАМИННІҢ НЕЙРОПРОТЕКТОРЛЫҚ ӘСЕРЛЕРІ

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D-пеницилламин (D-PA) бастапқыда гемолитикалық аурулар немесе бауыр уридин-5'-дифосфо-глюкуроносил трансфераза (UDP-глюкуроносил трансферазасы) ферменттерінің гемолитикалық аурулардан туындаған неонаталды гипербилирубинемияны емдеудегі ықтимал артықшылықтарына байланысты қолданылды. Сол кезеңде D-PA емін қабылдаған шала туған балаларда ретинопатияның (РОП) көп таралуы анықталды. Кейінірек зерттеу Польша, Венгрия, АҚШ, Мексика және Үндістандағы әртүрлі институттармен жүргізілді. Препаратты қысқа мерзімді немесе ұзақ мерзімді қолдану, уыттылықты немесе төзбеушілікті тудырмады, D-PA тіпті ересек емделушілерде қолданылған дозалармен салыстырғанда неонатальды кезеңде жоғарырақ дозаларда да берілді. Балалардағы билирубиннен туындаған кейбір неврологиялық дисфункциялар, оның ішінде ROP қоса алғанда және аутизм спектрінің бұзылыстары, металлдарды жинақтаумен, байланбаған билирубинмен (UCB) және орталық жүйке жүйесінің сезімтал аймақтарында мыс кешендері бар UCB тудыруы мүмкін. Эритроциттердің неонатальды гемолизі қанқұйылуы арқылы гематоэнцефаликалық тосқауылынан (BBB) өтетін қан жасушаларынан мыс пен темірдің физиологиялық емес бөлінуіне әкеледі. Содан басқа, белсенді оттегі түрлері ГЭБ өткізгіштігін арттырады, бұл нәрестелер миында қауіпті қатерлі шеңбер жасайды. Осы мақалада біз D-PA потенциалды нейропротективті әсерлеріне көрсететін жаңа туылғандар гипербилирубинемияның екі жағдайын ұсынамыз.

Негізгі сөздер: *D-пеницилламин; мыс; биллирубин; неврологиялық дисфункция; жаңа туылғандар ретинопатиясы; аутизм.*

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Introduction

Currently, 50% of pregnancies in the USA result in postnatal or prenatal mortality, considerable congenital disabilities, neurological developmental problems, or in other ways, chronically sick and unhealthy babies [7,28,9]. In recent years, the prevalence of immune reactive or neurotoxic conditions like attention deficit disorder (ADD), autism spectrum disorder (ASD), dyslexia, learning disabilities, as well as schizophrenia have increased rapidly [38,35,34]. In the organism, misplaced copper and iron ions catalyze the initiation and acceleration of the activity of oxygen radicals [31]. The interaction that exists between oxygen radicals and their target creates a free radical cascade. Free radicals attack and cause disruption of nearby cells, which additional will produce free radicals, and so on [30,23]. Reactive oxygen species and free radicals are drawn towards iron and copper ions [15,26], attack cells, disrupt cell membranes, neurotransmitters, neuroreceptors, and enzyme systems [32]. In particular, neuro-systems are vulnerable to peroxidative destruction since they have a high level of fat insulate. To this concept, ASD, ROP, and bilirubin-induced neurologic dysfunction (BIND) are neurodevelopmental and neurodegenerative diseases of the immature brain due to accumulation of unconjugated bilirubin (UCB), UCB-copper complex (as prooxidant), and free metals, respectively, in relevant brain parts, including the basal ganglia. The chelator D-penicillamine (D-PA) is an α-amino acid metabolite of penicillin without antibiotic properties (Fig. 1). D-PA can contribute to healthy cells through the reduction of free radicals via the removal of metal ions (in particular iron and copper), which catalyzes lipid peroxidation [3,16].

Furthermore, heme oxygenase activity, the peroxidation of lipid in the membranes of red blood cells and hemolysis, as well as the activity of uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase) prior to and after D-PA treatment can be described as critical areas for bilirubin excretion and production [19]. The

peroxidation of lipids also has been evaluated being a membrane damage mechanism in many hemolyses due to red cell disorders [12]. The susceptibility of red blood cells to autooxidation is three times higher in newborn babies compared with adults [37]. Also, a significant reduction in the fluorescence detection of cell lipid extracts and the hemolysis can be achieved by the in vitro D-PA preincubation [17]. It may be an acceptable drug to interact as a binding agent with the copper for use to control the occurrence of icterus neonatorum [17]. Although the same accurate information has been known over the last decades, the complete mechanism of D-PA action is still unknown.

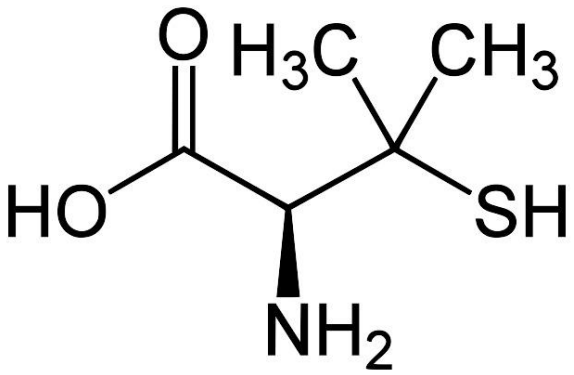

Fig. 1. The metal chelator D-penicillamine (dimethylcysteine, D-PA) is a metabolite of penicillin consisting a thiol, a carboxylic acid, and an amine.

We present two cases of neonatal hyperbilirubinemia from the Department of Pediatrics at Kenézy Gyula Hospital and Clinic in Debrecen, which indicate the potential neuroprotective effects of D-PA.

Case reports

Case 1.

The first patient was an AB0-incompatible preterm infant (birth weight: 2200 g.), who received treatment with D-PA during the neonatal time period [11]. Because of serious hemolysis, an early exchange transfusion was required, but not even this intervention was able to stop the rapid increase in the bilirubin level. At the beginning of the second exchange, the cardiopulmonary arrest occurred requiring resuscitation. At an extremely high bilirubin level (32.5 mg/dl) and with acute symptoms of bilirubin encephalopathy, the intravenous D-PA administration was started. After the first dose, a considerable fall of 6.5 mg/dl in the bilirubin level in four hours was observed, and due to the treatment, it was possible to observe that the hyperbilirubinemia gradually disappeared. Today, this patient is an opera singer and member of a famous German opera house. What makes this case even more remarkable is that neonatal hyperbilirubinemia frequently causes sensorineural hearing impairment.

Case 2.

It was cared for a term infant girl who was born at 39 weeks' gestation to a 24-year-old, blood group O, Rh-positive mother. The pregnancy was uncomplicated, and group A, an Rh-positive baby, weighed 3100 g. At 50 hours of age, the bilirubin level (Sebi) was 416 mmol/l (24.3 mg/dl); the hemoglobin value was 130 g/l. The baby was transferred to the neonatal unit, and the physicians decided to perform an exchange transfusion. At the admission, the baby's parents, who were members of the Jehovah's Witnesses, requested written in the chart that blood not under any circumstances, should be administered. On the other hand, they authorized the application of alternative therapies, i.e., 300 mg D-PA per day (divided into three doses) orally administered for three days, intravenous fluids, recombinant human erythropoietin (rhEPO), and phototherapy. The treatment with rhEPO was started with on day seven as a subcutaneous injection (200 U/kg) and was until day 23, given every second day, supplemented with vitamin E, folic acid, and iron. For this infant with ABO-HDN, the clinical data are shown in Table 1. Interestingly, she also has an excellent voice. At 16 years old, she was the winner of a school song festival. Also, she is a very good student in mathematics.

Table 1.

Clinical data of the reported infant (case 2).

Postnatal age	Serum bilirubin (µmol/l)	Hemoglobin (g/l)	Treatment
50 hours	416=24.3	130	D-PA+PT
58 hours	354=20.7		D-PA+PT
76 hours	277=16.2		D-PA+PT
100 hours	233=13.6	115	
Seven days	214=12.5	113	rhEPO
Nine days		95	rhEPO
12 days		87	rhEPO
15 days		98	rhEPO
20 days		101	rhEPO
25 days		120	
Six months		125	

Abbreviations: D-penicillamine (D-PA); physiotherapy (PT); recombinant human erythropoietin (rhEPO)

Discussion

Although many well-trained physicians have been practicing chelation in cases of neonatal hyperbilirubinemia also in Poland, and the USA [18,25,11,39,33], this therapeutic approach is still considered controversial. The use of D-PA as a copper chelator is accepted routinely for the treatment of Wilson's disease (WD), and it should then be initiated as soon as the disease is diagnosed, in many cases, in young children [14]. D-PA, as well as trientine, can reduce the copper content in the brain of experimental animals and in cases of WD, thereby preventing the development of severe neurological signs and symptoms [19, 8, 1].

Since D-PA is classified as an orphan drug by the U.S. Food and Drug Administration [13], intravenous D-PA is not sold in the normal drug market. Orphan drugs are pharmaceutical agents developed for the treatment of very rare medical conditions, which otherwise would not without support from the government been profitable to produce. These conditions are termed orphan diseases.

Already for more than two decades ago, it was known that the copper metabolism of fetuses is different from

adults and similar to WD [10]. This knowledge has led researchers to suggest that WD patients have an error in the change from the neonatal mode to the adult mechanism. Both in normal fetuses and in patients with WD, the biliary excretion of copper is considerable reduced, i.e., low plasma values of copper, as well as low or absent plasma concentration of caeruloplasmin [27].

Several heavy metal ions, in particular, iron and copper, have a crucial pathogenic role in neurodegenerative disorders, including BIND or other neonatal conditions, having an impact both on oxidative stress and the structure of proteins (misfolding) [4,5,6, 24]. A recently published long-term follow-up study [29] indicates that the administration of D-PA to newborn infants can give significant neuroprotection in severe cases of ROP and BIND. Also, oxidative stress and copper dyshomeostasis have been concerned with neurodevelopmental/neurodegenerative disorders like ASD. It is considered that elevated copper levels may be an etiological factor in ASD [40,2,20,36,21,22]. In newborn babies, the high activity of heme oxygenase may reflect the enzyme-inducing actions of metals (in particular copper and iron), which are derived by the breakdown of fetal erythrocytes [22].

Conclusion

D-PA is the most common drug for the treatment of copper overload. Also, some preterm infants have been treated with D-PA for severe jaundice and to prevent retinopathy during the last 28-40 years by Hungarian neonatologists. D-PA also alleviates oxidative stress and acts as a powerful antioxidant. D-PA also can reveal neuroprotective effects in BIND, and ROP, and may act protectively against other neurodegenerative disorders. However, it should be taken into account that D-PA may give rise to side effects. Monitoring of blood count, liver function tests, and urinary protein are recommended because of possible adverse effects.

Disclosure statement

All authors have no conflicts of interest to disclose.

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