Theranostics of
Brain, Spine & Neural Disorders
ISSN: 2641-8096

Juniper Publishers
key to the Researchers

Case Report
Volume 1 Issue 1 - May 2017
DOI: 10.19080/TBSND.2017.01.555552

Theranostics of Brain, Spine & Neural Disorders

Use of D-Penicillamine in the Neonatal Hyperbilirubinemias

György Balla, István Pataki and Lajos Lakatos*

Department of Pediatrics, University of Debrecen, Hungary

Submission: March 21, 2017; **Published:** May 05, 2017

***Corresponding author:** Lajos Lakatos, Department of Pediatrics, University of Debrecen 4032 Debrecen, Egyetem tér 1, , Hungary, Tel: +36 52 225335; Email: lakatosl@kenezykorhaz.hu

Abstract

D-penicillamine (DPA) was first recognized as a potential benefit for neonatal hyperbilirubinemia (NHBI) caused by hemolytic diseases 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 DPA. Later, our studies were replicated in other institutes in Hungary, Poland, U.S. A., 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 in the newborn period DPA was used 10-20 times higher doses than those in adult.

Keywords: D-Penicillamine treatment; ABO- and Rh hemolytic diseases; Orphan drug; Follow-up studies

Introduction

It appears that bilirubin IXα has unique structural properties which might have been predicted on the basis of modern concepts of organic chemistry but whose biological implications certainly were not fully appreciated [1]. The initial breakdown product of haemoglobin is UCB (unconjegated or indirect bilirubin) which is insoluble in water but soluble in lipids. This process is catalyzed by an important rate limiting enzyme, heme oxygenase (HO). UCB is carried in the blood bound to albumin. It is taken up by the liver and conjugated by the enzyme uridine 5'-diphospho-(UDP)-glucuronyltransferase to conjugated bilirubin (direct bilirubin) which is water soluble and excreted in bile into the gut and is detectable in urine when blood levels rise [2].

A. The term "kernicterus" is reserved for the chronic and permanent clinical sequelae of bilirubin toxicity.

B. There are no bilirubin levels which are known to be safe or which will definitely cause kernicterus or BIND.

C. "Vigintiphobia" = if the serum bilirubin concentration is 20 mg/dL (340 µmol/L); at a level at which ET was recommended.

In rhesus hemolytic disease (Rh-HDN), it was found that kernicterus could be prevented if the bilirubin was kept below 20mg/dL. 30-35 years ago this recommendation was applied to other hyperbilirubinemias as well. The guidelines are much more permissive now days [3] concerning jaundice at 2 days to 2 weeks of age. Some studies have found that the use of risk scores is as accurate as universal screening for predicting NHBI [4].

The age of onset is useful guide to the likely cause of the jaundice. Icterus starting within 24 hours of age usually results from hemolysis. This is particularly important to identify as the bilirubin is un conjugated and can rise very rapidly and reach extremely high levels. So, this condition requires close monitoring [5]. Jaundice occurring at 2 days to two weeks of age is usually due to other, more benign, causes but never be complacent.

When in the early 1970s, we reviewed the role of D-PA in the treatment of NHBI the drug was new to most neonatologists [6,7]. 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 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 [8]. D-PA has been found effective to decrease the concentration of bilirubin in blood samples *in vitro*. Subsequent clinical studies for control of NHBI was introduced to our department in March 1973. This drug, 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 [9].

Bizarrely, D-PA is a very cheap, low-cost drug, but at the same time it is developed under the Orphan Drug Act of 1983 in the U.S. which is a federal law concerning rare diseases (orphan diseases) [10]. This means that pharmaceutical companies produce this "homeless, not a money-maker" drug with reluctance. For example the IV form of D-PA is now a days not available in the market and the per os preparation is produced by a few companies in the world.

Dosages and use of D-PA in neonates

Safety and efficacy data regarding intravenous D-PA (Metalcaptase^{R}) use in neonates have not been available. So, we had to establish the safe portions and the adequate UCB-lowering doses. When we have observed a favorable clinical outcome occurred in all cases with NHBI without side effects (no patient had or developed renal impairment or other not desired adverse effects), we have decided to use an unusually high IV administration of this drug Table 1.

Table 1: Dosages and use of D-PA in neonates.

3x 100mg/kg b.w. IV for 3-7 days
in the neonatal jaundice + once daily50mg/kg b.w.iv
Untill the end of the second week of life to prevent ROP

The bioavailability of intravenously administered drug is 100% since no absorption process is involved. The rate of absorption of orally administered drugs is slower in neonates and young infants due to delayed gastric emptying resulting to prolongation in time required to achieve maximal plasma concentration. In the early period of D-PA therapy we used lower doses and, observing the lack of any adverse effects, we raised the dose gradually until the achievement of optimal bilirubin decrease. Compared with older children and adults, neonates have significant differences in physiology affecting drug absorption, distribution, metabolism, and elimination. Fortunately, the developmental pharmacology and the age related effects of D-PA largely favoured by the administration of unusually high doses of this drug [11].

In this survey we will review our D-PA research, which embraces a period of more than 40 years. We intend to focus on only a few aspects of this field which we feel to be important.

D-PA therapy in various hyperbilirubinemias of the newborn infant

Table 2. shows the effects of DPA-therapy in ABO- Hemolytic Disease of the Newborn (HDN) in term infants (IV administration starting at <24 hours of age – group I). In the ABO-HDN, D-PA significantly reduced the need for both initial and repeated ETs. The number of ET per infant was 1.32 in the control and 0.11 in the treated group. The infants who received D-PA therapy had significantly lower mean serum bilirubin (SEBI) concentrations than the control infants [12]. In the group II (25 treated and 27 control infants) D-PA therapy was started after the third day of life. In group I D-PA caused a marked decline of SEBI concentrations at a time when such levels were rised in the control infants. II D-PA considerably reduced the number of ETs (0.70 : 0.24 = control : treated) but the difference was statistically not significant. In the latter patients the mean bilirubin values showed a smaller difference compared to the controls than in group I. Since group I represented the results of early or preventive treatment, while group II those of late or therapeutic treatment, it is obvious that, for ensuring success, D-PA treatment should be begun as early as possible in AB0-HDN.

Table 2: D-PA in ABO-HDN of term infants.

(Iv Administration Starting at <24 Hours of Age)		
	DPA- Groups	**Controls**
N (M:F)	34 (15:29)	34 (12:22)
Cord bilirubin	3.9	3.9
Serum bilirubin <24 hs	11.1	11.9
Peak bilirubin at 48-72 hs	15	18.4
Exchange transfusions	3 (X:0.11)	25 (X:1.3)

In Rh-HDN the number of ET per infant was 1.6 in the control and 0.7 in the treated group. In addition almost the half of cases no ET was performed in the D-PA-treated group11Table 3 [13].

Hyperbilirubinemia

Table 3: D-PA in Rh--HDN of term infants.

DPA Groups		
N (M:F)	30 (18:12)	33 (19:14)
Cord bilirubin (mg/dL)	3.9	4.2
Serum bilirubin <24hs	11.2	12.3
Peak bilirubin at 48-72 hs	14	15.6
Exchange transfusions	21 (X:0.7)	52 (X:1.6)
ET was not performed	43.30%	6%

In another clinical study [14] we examined the ability of D-PA therapy to modify the course and duration of so-called idiopathic hyperbilirubinemia in term infants in comparison with ETs (Table 4). Patients were randomly selected to receive D-PA therapy or ET when the SEBI reached values of more than 20 mg/dL. It is to be noted that ET was also performed in cases treated with D-PA where the level of bile pigment did not decrease within 4-6 hours after the first single intravenous dose. No infants studied had any laboratory or clinical evidence of illness or hemolytic process or any sings of disturbances of the central nervous system (CNS). It was found that infants who received ET had a significantly lower SEBI 8-12 hours after intervention than infants in the DPA-treated group, but there was no significant difference between the two groups at 32-36 hours of the post exchange period, respectively.

In the course of conducting clinical trials to investigate the presumably beneficial effects of D-PA in the reduction of

How to cite this article: György B, István P, Lajos L. Use of D-Penicillamine in the Neonatal Hyperbilirubinemias. Theranostics Brain,Spine & Neural Disord. 2017; 1(1): 555552. DOI: 10.19080/TBSND.2017.01.555552

retinopathy of prematurity (ROP), we routinely measured the SEBI of VLBW infants. There was no significant difference between the D-PA-treated and control groups either in the mean peak SEBI or in the number of ETs needed [15]. This suggests phototherapy alone proved to be just as effective as phototherapy plus D-PA in babies with a birth weight under 1500g Table 5. The most frequent clinical factors in the severity of NHBI of VLBW infants include increasing immaturity, unrecognized neonatal hemolysis, array of genetic conditions or concurrent conditions of dehydration, sepsis, or acidosis, hypoalbuminemia, and/or poor feeding. With current clinical practice, icteric complications are exceedingly infrequent given the liberal, prophylactic, and effective use of phototherapy.

Table 4: D-PA Therapy vs ETs in the treatment of idiopathic.

	DPA Groups	Controls
N (M:F)	23 (11:12)	22 (12:10)
Serum bilirubin (mg/dL)		
Before Interventions	21	21.9
8-12 hs after interv.	20	17.9
32-36 hs after interv.	18.2	17.6
Ets	4	24

Case Reports

There were some very impressive cases in our practice in neonatology deserved to show them individually. The first patient received D-PA treatment in the neonatal period was an AB0-incompatible preterm infant with birth weight of 2000 g. At an extremely high TSB (32.5mg/dL) intravenous administration of D-PA was begun. The first dose caused a spectacular fall of 6.5mg/dL in the level in 4 hours, and under the influence of such treatment we were able to witness a gradual disappearance of the NHBI. She is now a member of a famous operhouse in Germany as an opera singer Table 7. This case is all the more remarkable because this baby showed typical symptoms of acute bilirubin encephalopathy at 3-6 days of age: somnolence, hypotonia, and loss of the Moro reflex and sometimes opisthotonus. In addition, she was in need of CPR (cardiopulmonary resuscitation) just at the beginning of the ET because of a cardiac arrest, so, the intervention (ET) was not performed and it proved to be unsuccessful concerning the high UCB level. Surviving of the neonatal period, however, she did not demonstrate any of the chronic manifestations of bilirubin encephalopathy, including the most common sequelae of sensorineural hearing imperment [16]. The lack of chronic (residual) symptomes is due to the neuroprotective effects of D-PA in the neonatal period. In 1999 we published a case of an AB0 incompatible term infant girl born to parents who were Jehovah's Witnesses [17]. The infant was admitted to our neonatal unit with a high SEBI necessitating ET. The parents signed a request that blood should not be administered under any circumstances. However, they authorised us to use of alternative treatments: orally administered D-PA, phototherapy, intravenous fluids, and recombinant human erythropoietin (200U/kg bw. subcutaneously on every second day for two weeks). This infant was discharged from our unit in good health. Her physical growth and motor milestones at 3 years of age revealed no red flags for neurodevelopmental maturation. In addition, the follow up audiometric tests performed on this infant were normal. She was the first baby in the world who received such a combined alternative (and "bloodless") treatment for serious AB0-HDN.

Table 5: Effect of Phototherapy (PhT) and DPA vs PhT in Infants <1500 g.

	PhT+D-PA	PhT
N (M:F)	25 (12:13)	23 (12:11)
Serum bilirubin (mg/dL)		
Before treatments	9.8	10
Peak bilirubin at 5-6 days	12.2	12.8
Ets	5	6

We recently cared for a term infant boy blood group B, Rh-positive who was born at 37. gestation to a 33-year old, blood group B, Rh-negative mother [18,19].The baby was born as an 11. offspring of his mother and appeared jaundice at 10 hours of life and had moderate anemia. The direct Coombs test was strongly positive (++++) in the cord blood. The clinical characteristics of the infant with Rh-HDN are shown in the Table 6.

Table 6: Treatment of an infant with Rhesus-HDN without ET.

Serum Bilirubin	Hemoglobin
at 12 hs: 12.2	119 g/L
at 58 hs: 19.4	108
at 9 days: 2,8	67 (50ml PRBC)

Table 7: Methods testing the possible bilirubin displacing effect of D-PA.

S.no	Methods
1	Sephadex method
2	Peroxidase technique
3	MADDS (Monoacetyldiamino-diphensulfone) method
4	Investigations in Gunn-Rats

Before we attempt to summarize the possible mechanisms of action of D-PA in the neonatal period, it is appropriate to elucidate its interference with the binding of UCB to human serum albumin. Such testing seems to be particularly necessary with a plasma bilirubin-lowering drug, since theoretically the effect might be explained by displacement of the pigment from its albumin binding. We performed detailed investigations using three *in vitro* methods in addition two *in vivo* testing in Gunn rats. Results were negative in all cases (Table 7). Quantitatively, the doses of D-PA administered to the neonates do not displace UCB from its binding to albumin. Consequently, the ameliorating effect of D-PA on NHBI must be due to other mechanisms [20].

Mechanisms of Action of D-PA in the Neonatal Hyperbilirubinemia

Since heme metabolism is a crucial stage in bilirubin production, we examined the activity of heme oxygenase, the initial and rate-limiting enzyme of heme degradation [21,22]. The 3 days of DPA

How to cite this article: György B, István P, Lajos L. Use of D-Penicillamine in the Neonatal Hyperbilirubinemias. Theranostics Brain,Spine & Neural Disord. 2017; 1(1): 555552. DOI: 10.19080/TBSND.2017.01.555552

treatment in the adult animals did not lead to any significant change in heme oxygenase activity. In contrast, in neonates a marked reduction in enzyme activity was observed following DPA treatment. At the same time, the activity of UDP glucuronyltransferase was measured in liver homogenates of newborn and adult rats. After DPA treatment we could not observe any changes in enzyme activity [23,24].

The plausible explanation of age-relating mechanisms of action of DPA: bilirubin production will be inhibited by the decreased activity of heme oxygenase. The age-related differences in the effect of DPA concerning heme oxygenase is supported by the experimental works of Maines & Kappas [25].

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Other beneficial effects of D-PA, together with bilirubin, in the neonatal period are as follows: neuroprotection against copper-induced oxidative/nitrosative stress and excitoxicity in the neonatal period [26].

References

1. Schmid R (1978) Bilirubin metabolism: state of the art. Gastroenterology 74: 1307-1312.
2. Pandey R, Dwivedi MK, Gupta S (2015) Screening of Liver Diseases in Urban Areas with Special Reference to Bilirubin and Iron.
3. Muchowski KE (2014) Evaluation and Treatment of Neonatal Hyperbilirubinemia. Am Fam Physician 89(11): 873-878.
4. Bhutani VK, Stark AR, Lazzeroni LC, Poland R, Gourley GR, et al. (2013) Predischarge screening for severe neonatal hyperbilirubinemia identified infants who need phototherapy. J Pediatr 162(3): 477-482.
5. (2009) Statewide Maternity and Neonatal Clinical Guidelines Program. Neonatal jaundice prevention, assessment and management.
6. Lakatos L, Kövér B (1974) Az újszülöttkori hyperbilirubinaemiák D-Penicillamin therapiája. D-Penicillamine Therapy In Neonatal Hyperbilirubinaemias. A Preliminary Report. Orv Hetil (Hungarian J Med) 115: 307-311.
7. Lakatos L, Kövér B, Péter F (1974) D-Penicillamine Therapy of Neonatal Hyperbilirubinaemia. Acta Paediatr Acad Sci Hung 15: 77-85.
8. Manuel O, Araya M, Uauy R (2000) Copper Homeostasis in Infant Nutrition: Deficit and Excess. J Pediatr Gastroenter Nutr 31(2): 102-111.
9. Korányi G, Kovács J, Vörös I (1978) D-Penicillamine treatment of hyperbilirubinemias of preterm infants. Acta Paediatr Acad Sci Hung 19: 9-14.
10. Orphan drug - Wikipedia, the free encyclopedia.
11. Ku LC, Smith PB (2015) Dosing in neonates: Special considerations in physiology and trial design. Pediat Res 77: 2-9.
12. Lakatos L, Kövér B, Oroszlán G, Vekerdy Z (1976) D-Penicillamine Therapy in AB0 Hemolytic Disease of the Newborn Infant. Europ J Pediat 123(2): 133-137.
13. Lakatos L, Kövér B, Oroszlán G (1976) D-Penicillamin kezelés Rh-isoimmunisatio okozta, újszülöttkori haemolytikus betegségben. (D-Penicillamin therapy in Rh-haemolytic disease of the newborn infants). Gyermekgyógyászat (Hungarian J of Pediatrics) 27: 307-310.
14. Lakatos L, Oroszlán G, Lakatos Z (1989) D-Penicillamine in the Neonatal Period. In: Physiologic Foundations of Perinatal Care Eds, New York-Amsterdam, London, 3: 188-197.
15. Lakatos L, Hatvani I, Oroszlán G, (1986) Controlled trial of D-penicillamine to prevent retinopathy of prematurity. Acta Paediat Acad Sci Hung 27: 47-56.
16. Worley G, Erwin CW, Goldstein RF, Provenzale JM, Ware RE, et al. (1996) Delayed development of sensorineural hearing loss after neonatal hyperbilirubinemia: a case report with brain magnetic resonance imaging. Dev Med Child Neurolog 38(3): 271-277.
17. Lakatos L, Csáthy L, Nemes É (1999) "Bloodless" treatment of a Jehovah's witness infant with AB0 hemolytic disease. J Perinatol 19(7): 530-533.
18. Nagy A, Lakatos L (2005) D-penicillamine treatment in Rh-Haemolytic Disease of a newborn. Arch Dis Child (online publication).
19. Lakatos L (2004) Bloodless treatment of infants with Haemolytic Disease. Arch Dis Childh 89(11): 1076-1076.
20. Brodersen R (1974) Competitive binding of bilirubin and drugs to human serum albumin studied by ensymatic oxidation. J Clin Invest 54(6): 1353-1364.
21. Brodersen R, Lakatos L, Karmazsin L (1980) D-Penicillamine, a non-bilirubin-displacing drug in neonatal jaundice. Acta Paediatr Scand 69(1): 31-35.
22. Bakken AF, Thaler MM, Schmid R (1972) Metabolic Regulation of Heme Catabolism and Bilirubin Production. I. Hormonal control of hepatic heme oxigenase activity. J Clin Invest 51(3): 530-536.
23. Oroszlán Gy, Lakatos L, Szabó L (1983) Heme oxygenase activity is decreased by D-Penicillamine in neonates. Experientia 39: 888-889.
24. Maines MD, Kappas A (1977) Metals as regulators of heme metabolism. Science 198: 1215-1221.
25. Lakatos L, Balla G (2016) From the image towards a new concept. Metabolic Brain Disease 31: 485-486.
26. 26. Lakatos L, Balla G, Pataki I (2017) Copper-induced oxidative/nitrosative stress and excitoxicity in the neonatal period: neuroprotection with D-Penicillamine. Pediatric Dimensions in press.

DOI: 10.19080/TBSND.2017.01.555552

How to cite this article: György B, István P, Lajos L. Use of D-Penicillamine in the Neonatal Hyperbilirubinemias. Theranostics Brain,Spine & Neural Disord. 2017; 1(1): 555552. DOI: 10.19080/TBSND.2017.01.555552