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D-Penicillamine in the Neonatal Period: Case Reports

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

D-Penicillamine (DPA) was first recognized as a potential benefit for neonatal hyperbilirubinemia (NHBI). 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 (3 x 100 mg/kg bw./day IV for 3-7 days in the neonatal jaundice + once daily 50 mg/kg bw. IV until the end of the second week of life to prevent ROP) than those in adult. There were some very impressive cases in our practice in neonatology which deserved to be shown individually.

Keywords: D-Penicillamine; neonatal hyperbilirubinemia; retinopathy of prematurity.

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ABBREVATIONS

DPA -D-Penicillamine
ET -Exchange transfusion
HDN -Hemolytic Disease of the Newborn
IV -Intravenously
NHBI -Neonatal Hyperbilirubinemia
PBRC -Packed Red Blood Cells
ROP -Retinopathy of Prematurity
SEBI -Serum Bilirubin Concentration
UDP -Uridine Diphosphate (-glucuronyltransferase)
VLBW -Very Low Birth Weight

1. INTRODUCTION

When in the early 1970s, we reviewed the role of D-Penicillamine (DPA) in the treatment of NHBI [1], the drug was new to most neonatologists. The idea that DPA 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 [2]. It is well known that all neonates have increased concentration of copper in the liver and a decreased concentration of a specific plasma copper-protein, ceruloplasmine, in comparison with individuals over one year old.

In the newborn period DPA was used 10-20 times higher doses (3 x 100 mg/kg bw./day intravenously /IV/ for 3-7 days in the neonatal jaundice + once daily 50 mg/kg bw. IV until the end of the second week of life to prevent ROP) than those in adult.

2. CASE REPORTS

The first patient received DPA treatment in the neonatal period was an AB0-incompatible preterm infant (2200 g bw.). At an extremely high serum bilirubin concentration (SEBI: 32.5 mg/dL) and, signs of various neurological dysfunction, intravenous (IV) administration of DPA was begun. The first dose caused a spectacular fall of 6.5 mg/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 [3]. This case is all the more remarkable as the most common sequelae of NHBI is the sensorineural hearing impairment [4].

In 1999 we published a case of an ABO incompatible term infant girl born to parents who were Jehovah's Witnesses [5]. The infant was admitted to our neonatal unit with a high SEBI necessitating ET, her physical and neurological status, however, was good. The parents signed a request that blood should not be administered under any circumstances. However, they authorised the use of alternative treatments: orally administered DPA, phototherapy, intravenous fluids, and recombinant human erythropoietin (200 U/kg 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.

We recently cared for a term infant boy blood group B, Rh-positive who was born at 37. weeks of gestation to a 33-year old, blood group B, Rh-negative mother [6]. The baby was born as the 11th offspring of his mother and appeared jaundice at 10 hours of life and had moderate anaemia. No sign of neurological dysfunction. 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 1.

2.1 D-Penicillamine a Non-bilirubin Displacing Drug in the Neonatal Period

It is appropriate to elucidate drug's interference with the binding of bilirubin to human serum albumin. We performed detailed investigations using three *In vitro* methods (Sephadex method, Peroxidase technique, MADDS /monoacetyldiamino-diphenylsulfone/ method) in addition to two *In vivo* testing in Gunn rats [7].

Table 1. Treatment of an infant with Rhesus-HDN without ET

Term infant boy was born as an 11. offspring of his other at 37. gestation with 3100 g bw. Cord blood: Direct Coombs test strongly positive, bilirubin level: 4.2 mg/dL	
SEBI	**Hemoglobin**
at 12 hs: 12.2	119 g/L
at 58 hs: 19.4	108
at 9 days: 2,8	67 (50 ml PRBC)
Th.: photherapy + DPA started at 12 hours of life for 5 days	

Results were negative in all cases. Quantitatively, the doses of DPA administered to the neonates do not displace bilirubin from its binding to albumin.

2.2 Mechanisms of Action of D-Penicillamine in the Neonatal Hyperbilirubinemia

The complete mechanism of action of DPA is still unknown, but some interesting pieces of information have been unfolded over the last decades. Three crucial areas of bilirubin formation and excretion have been investigated in our laboratory: The lipid peroxidation of the red blood cell membrane and hemolysis; heme oxygenase activity and UDP-glucuronyltransferase activity before and after DPA treatment. Lipid peroxidation has been considered to be a mechanism of membrane damage in a number of red cell disorders leading to hemolysis [8]. The susceptibility of red cell lipids to autooxidation is about three times as high in the newborn as in adults [9]. *In vitro*, the preincubation with DPA resulted in a significant decrease of both the hemolysis and fluorescence of red cell lipid extracts [10].

In vivo, pretreatment with DPA has prevented the phenylhydrazine-induced lipid peroxidation in rats [11]. Malondialdehyde is a product of lipid peroxidation resulting in disintegration and disruption of biologic membranes. The binding of DPA to malondialdehyde may prevent this process [12].

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. The 3 days of DPA 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.

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 and Kappas [13]. The high activity of heme oxygenase in the newborn could reflect the enzyme-inducing action of metals derived from the breakdown of fetal erythrocytes. Chelation therapy in neonates restores the normal activity of enzymes participating in heme metabolism [14].

Thus, chelating agents facilitate heme synthesis and inhibit heme degradation [15].

In the light of the foregoing we present our clinical observations in Fig. 1. The effect of a single 100 mg/kg body weight intravenous dose of DPA on SEBI in premature and term infants can be seen 4-6 hours after the administration. A rapid decrease in SEBI was observed only in term infants with high SEBI, but DPA has not had any effect in prematures under 1500 g birth weight (the WLBW infants suffering from so called accumulating NHBI due to immaturity of glucuronyltransferase enzyme system) and term infants with low SEBI. A plausible explanation for this is that DPA inhibits bilirubin formation but it does not cause any change in UDP-glucuronyltransferase activity. In cases with high bilirubin in term infants, however, the marked decrease observed was due to enzyme induction by bilirubin itself, which had gradually increased during the previous days in these babies [16].

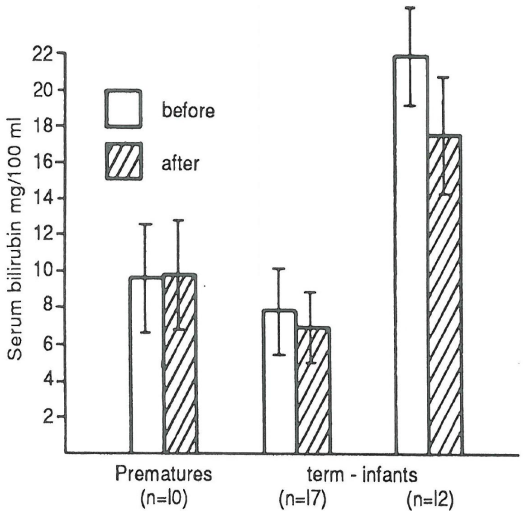

Fig. 1. Effect of a single dose of D-Penicillamine in 4-6 hours after intravenous administration

3. CONCLUSIONS

During the last 40 years Hungarian neonatologists have treated approximately a number of term and preterm infants with DPA to treat severe jaundice and prevent retinopathy.

No acute or long-term adverse effects or any late complications of this treatment protocol have been observed during several years of follow-up. According to our opinion, the most important „discovery" of DPA-project is that this drug should be undoubtedly effective (jaundice, ROP and lead burden in neonates), safe (more than 25-30 000 cases only in Hungary without any side effects!) and quite inexpensive (even more for the developing countries!), and it can be used in unusual high doses in the neonatal period.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

All experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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