

Short Communication

Exchange Transfusion-To do or Not to do for Neonatal Hyperbilirubinemia?

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Abstract

Exchange transfusion for the treatment of neonatal hyperbilirubinemia is frequently used also in the low- and middle-income countries. This unique intervention in the neonatal period is rather aggressive and too expensive method as a therapy of a generally harmless disease. In neonates the chelating effects of D-Penicillamine (D-PA) play also important role: (i) in attenuating the oxidative stress, (ii) in the transient inhibition of heme oxygenase enzyme resulting in a decrease of bilirubin production, and (iii) the age-relating effects of D-PA. Transition biometals now are in the focus of the etiopathogenesis of neurodegenerative and neurodevelopmental diseases (NDs) including the bilirubin-induced neurologic dysfunction (BIND). The “relatively” early diagnosis of jaundice takes suitable neonates for a short time (300 mg/kgbw per os, divided into three parts daily, for 2-5 days) D-PA treatment. It may be affordable especially in poorly resourced countries.

Keywords: D-Penicillamin; Hyperbilirubinemia; Exchange transfusion; Poorly resourced countries

1. Introduction

In 1999, a provocative letter was written to persuade others to perform multicentre prospective randomized controlled clinical trials with the project of ~Prevention of Exchange Transfusion (ET) and Retinopathy of Prematurity (ROP) by D-Penicillamine (D-PA)~ [1].

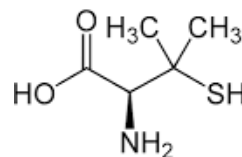


Figure 1: Structural formula of D-PA.

The chemical behavior of this drug can be discussed in terms of three types of reaction: formation of (1) disulfide bridges, (2) thiazolidine rings, (3) metal complexes and chelates [2]. Metal ions accumulate in the brain with aging and in several neurodegenerative diseases (NDs). In the neonatal period the chelating effects play also important role: (i) in attenuating the oxidative stress, (ii) in the transient inhibition of heme oxygenase (HO-1) enzyme resulting in a decrease of bilirubin production, and (iii) the age-relating effects of D-PA [1]. Transition biometals now are in the focus of the etiopathogenesis of neurodegenerative and neurodevelopmental diseases (NDs) [3] including the bilirubin-induced neurologic dysfunction (BIND) in the neonatal period [4].

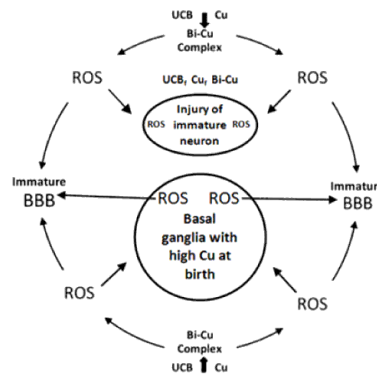


Figure 2: Molecular mechanism of BIND [4] (UCB-unconjugated bilirubin; UCBf-free unconjugated bilirubin; Cuf-free Cu; ROS-reactive oxygen species; BBB-blood brain barrier).

The neuropharmacological actions of metal-targeted agents most likely arise from *local metal redistribution rather than from massive metal removal* [5]. This goal may be achieved by abolishing abnormal metal/protein interactions, by contrasting localized metal excesses, by normalizing intra/extra cellular metal ratios or by restoring the correct balance among the main biometals: Cu, Fe, and Zn [6-8].

2. History and Protocol of Neonatal Exchange Transfusion

Neonatal hyperbilirubinemia (NHBI) is the most common condition (or symptom) in the first two weeks of postnatal life. Although generally harmless, some neonates may develop very high levels of total serum bilirubin level (TSB). Subtle encephalopathy or BIND refers to individuals with subtle neurodegenerative or neurodevelopmental damage.

- The term “acute bilirubin encephalopathy” is used to describe the acute manifestations of bilirubin toxicity.
- The term “kernicterus” is reserved for the chronic and permanent clinical sequelae of bilirubin toxicity.
- It is very difficult task to recognize which bilirubin levels are safe or which will definitely cause kernicterus or BIND.
- “Vigintiphobia”=if the serum bilirubin concentration is 20 mg/DL (340 μmol/L); at a level at which double volume exchange transfusion (ET) was recommended.

In rhesus hemolytic disease (Rh-HDN), it was found that kernicterus could be prevented if the TSB was kept below 20 mg/dL [9]. 30-35 years ago this recommendation was applied to other NHBI as well. The guidelines are much more permissive nowadays concerning jaundice at 2 days to 2 weeks of age [10, 11].

3. The Neuroprotective Effects of Intravenously (or orally) Administered D-PA can make ETs Unnecessary?

On the basis of our current knowledge, it is impossible to respond this question. Situations may arise, however, in the practice of neonatology, when the TSB is higher than the ET-compatible bilirubin values, and in these cases we have to apply alternative therapy (intensive phototherapy, drugs, including D-PA et cet.). In the retrospectively screening (in our 3 follow-up studies) these babies were examined at 1-44 years of age. *They showed better somatic and mental development than the controls* (the average Hungarian population without ET). In the Table 1, three particular interesting a convincing cases are demonstrated. Relevant data of their neonatal period were published in details earlier [12-14].

Variables	Case of K.É	Case of J.W	Case of H.E
Sex	Female	Female	Male
Birth weight (g)	2200	2700	3100
Gestation (weeks)	33	37	39
Blood group incomp.	ABO-HDN	Rh-HDN	ABO-HDN
Direct Coombs-test	NP	++++	NP
Cord bilirubin (mg/dL)	NA	4.2	NA
Peak bilirubin (mg/dL) at hours	32.5 at 72	24.3 at 50	19.5 at 58
Hemoglobin (g/L)	90.0 at 72	113.0 at 168	67.0 at 216
D-PA treatment (daily)	IV 300 mg/kgbw	p.o.300 mg/kg	p.o. 300 mg/kg
Phototherapy	-	+	+
Anemia “correction”	60 ml PRBC	Rh-erythropoetin	60 ml PRBC 200 U/kgbw
Last follow up (at years of age)	44	18	18
Quality of life	Opera singer	Excellent in the school	Suitable for a bad social situation

(HDN-Hemolytic disease of the newborn; NP-Not performed; NA-Not available; IV-intravenously; PRBC-Packed red blood cells; Rh-erythropoetin-recombinant human erythropoietin.)

Table 1: Three, particular interesting cases in the praxis of Debrecen NICU (K.É.-ET was finished because of cardio respiratory arrest; J.W.-parents signed a request that blood should not be administered under any circumstances; H.E.-orally D-PA proved to be effective in early stage of ABO-HDN).

4. Conclusion

The “relatively” early diagnosis of hyperbilirubinemia takes suitable neonates for a short time (300 mg/kgbw per os, divided into three parts daily, for 2-5 days) D-PA treatment. It may be affordable, especially in poorly resourced countries [15].

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