

Review

D-penicillamine in the neonatal period: A cost-effective approach to HIV-positivity due to vertical transmission

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D-penicillamine (DPA) was first recognized as a potential benefit for neonatal hyperbilirubinemia (1974-1980) in the Department of Neonatology of Medical University of Debrecen, Hungary. During this time, there was a remarkably low incidence of retinopathy of prematurity (ROP) in the infants treated with DPA. Later, studies by this author was replicated in other institutes in Hungary, and in the U.S., and India. 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 in adult. On the basis of American research work concerning the beneficial effect of DPA-therapy in adult AIDS-patients, it would be reasonable to treat neonatal HIV-positivity due to vertical transmission with short-term DPA therapy.

Key words: D-penicillamine, neonatal, retinopathy of prematurity (ROP), therapy.

INTRODUCTION

In developing countries, especially in Africa, the epidemic of heterosexually transmitted HIV infection is a major health problem together with the increased HIV-associated infant mortality rate. D-penicillamine (DPA) has been on the market for over 60 years. Bizarrely, DPA is a very cheap, low-cost drug, but it is developed under the Orphan Drug Act of 1983 in the U.S. which is a federal law concerning rare diseases (orphan diseases). This means that the pharmaceutical companies produce this "homeless, not a money-maker" drug with reluctance. For example the IV form of DPA is nowadays not available in the market and the oral preparation is produced by few pharmaceutical companies in the world (en.wikipedia.org/wiki/Orphan_drug).

DPA was first recognized as a potential benefit for neonatal hyperbilirubinemia (1974-1980) in the Department of Neonatology (Lakatos et al., 1976). During this time, a remarkably low incidence of retinopathy of prematurity (ROP) was noticed in the infants treated with DPA. In the 1980s, a series of articles was published in the Hungarian and International literature concerning the use of DPA for these conditions, including two randomized trials. A Cochrane review of the date in 1998 said that there was "clearly sufficient evidence to justify

further investigation" (Phelps et al., 2001; Lakatos et al., 1999). Later, studies by this author was replicated in other institutes in Hungary (Korányi et al., 1978), and in the U.S. (Christensen et al., 2007) and India (Tandon et al., 2010). It is important to note that there was no intolerance or short- or long-term toxicity of the medication (Vekerdy-Lakatos et al., 1989) in spite of the fact that in the newborn period, DPA was used 10-20 times higher doses than in adult (3 × 100 mg/kg b.w. IV for 5 days in the neonatal jaundice). Furthermore, DPA was used once daily at a dose of 50 mg/kg b.w. IV until the end of the second week of life in order to prevent ROP in VLBW-infants.

LITERATURE REVIEW

Searching the pertinent literature, several publications relating to the beneficial effects of DPA-therapy in the treatment of AIDS-patients were found. The high doses resulted in good outcomes, but adult patients did not tolerate this therapy. In addition to this, it has been determined that the selective inhibition of replication of HIV type 1 (further: HIV) by this drug was concentration dependent, that is, at 40 microgram/ml concentration,

DPA completely inhibited HIV replication in H9 cells *in vitro* (Scheib et al., 1987). As mentioned above, it is possible to use very high doses of DPA in neonates during short-term therapy, without any harmful adverse effects (a single 100 mg/kg b.w. IV administered DPA resulted in more multiple plasma concentration in premature infants) (Oroszlán et al., 1987). So, this study has another promising idea wondering whether or not it is true that DPA has possible beneficial effects on the AIDS associated infant mortality rate because of its prolonged antiviral activity tested in adults suffering from AIDS (Lakatos, 2000). In the adult patients with rheumatoid arthritis, the therapeutic regime is “go low - go slow”; on the contrary, “go high for a while” is in the neonates.

In this study, a question is raised: what are the reasons as to why newborn can withstand the dose and adults can not? The incidence of toxicity from DPA in rheumatic patients is of the order of more than 20% during long-term treatment. They have a background of a disturbed immune system in contrast to patients with Wilson's disease and neonates. Thus one can conceive that in rheumatoid arthritis, a haptenic antigen may be formed in which the hapten is the DPA combined with a variety of proteins and paraproteins causing various autoimmun disturbances (Hill, 1979).

Abundant experimental evidence and clinical observations exist to suggest that early viremia and immune responses in vertical HIV infection are different from those of adults. The developing immune system might allow for more efficient viral replication and less efficient immune containment of viral replication. In this respect, DPA-therapy may be a potent early regime to control HIV replication and offers the golden opportunity to prevent or reverse the rapid progression of this disease.

The potential mechanism of antiretroviral actions of DPA in HIV-infection caused by vertical transmission are as follows:

- It is presumed that antioxidant treatment (DPA is a well-known strong antioxidant) may provide a promising and cost-effective therapeutic approach in treating neonatal HIV infection. The newborn infants, especially the prematures, are suffering, that is, in an oxidative stress condition (Kashou and Agarwal, 2011).
- It acts as a potent protease inhibitor in animal model (Norga et al., 1995).
- The copper metabolism in Wilson's disease and in newborn infants is strikingly similar: they both have large quantities of copper in the liver and low ceruloplasmine in the blood. It was previously found that cupric chloride, in the presence of a chelating agent, could inhibit the HIV-1 protease (Davis et al., 1995).
- Extra cystein given in the form of DPA (dimethyl cysteine) can cause an increase in intracellular cysteine and glutation content which play an important role as HIV inhibitors, at least in part because they facilitate the

intracellular transport of Zn and Cu ions (Sprietsma, 1999).

- The HIV-1 nucleocapsid p7 protein contains two retrovirus-type zinc finger domains that are required for multiple phases of viral replication. Considering the chelating properties of DPA and its disulfide reaction with cysteine, one can conclude that HIV-replication could be inhibited by this drug (Shi and Berg, 1995).

It would be very exciting to be involved in this work, especially since a pilot study (5 babies) could be enough to prove that DPA will have a huge impact on HIV infection caused by vertical transmission.

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