Biology of Bilirubin Photoisomers

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KEYWORDS

• Phototherapy • Jaundice • Neonatal • Bilirubin • Bilirubin photoisomers • Solubility • Toxicity • Membrane permeability

KEY POINTS

- Phototherapy converts bilirubin to more polar, thus water-soluble, photoisomers. They are excreted in urine and bile, but the excretion profile varies between isomers.
- Physical and biological arguments point to lesser toxicity for bilirubin photoisomers than for native bilirubin-IXα (*Z,Z*), but in vitro evidence is controversial.
- Given the increased polarity of bilirubin photoisomers, they should be less prone to cross the blood–brain barrier, but no experimental evidence is available to support this hypothesis.
- Phototherapy may not be innocuous in the smallest, most immature infants; whether this is related to aspects of irradiation or the profile of the bilirubin isomer mix, including photo-oxidation products, is unknown.

INTRODUCTION

Jaundice from unconjugated hyperbilirubinemia is arguably the most common reason for diagnostic and therapeutic interventions in newborn infants. Estimates for usage rates in healthy, term infants are mostly in the 2% to 6% rate, depending inter alia on which national guidelines are being used, and also on local practice patterns.[1] In a recent prospective 1-year study of phototherapy use in Norwegian neonatal intensive care units (NICUs), we found that among premature infants at less than 28 weeks gestational age, more than 80% received phototherapy at some point during their NICU stay.[2]

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Since the discovery of phototherapy to treat neonatal jaundice,[3] this therapeutic modality is now probably available in all newborn departments as well as maternity wards in the industrialized world. The first phototherapy devices were "home-made" and rather crude.[3] The devices have, in the ensuing 50 years, undergone several stages of advancing technological development. Currently, phototherapy devices using light-emitting diodes seem to be the most widespread, at least in the industrialized part of the world. At the same time, work is ongoing to increase access to phototherapy in low- and middle-income countries by creating much simpler devices that use sunlight and optic filters rather than being dependent on solely electricity and lamps or tubes.[4]

Phototherapy was for a long time regarded as quite harmless, and studies of how it has been used evinced a wide scatter of practical applications.[5,6] This heterogeneity may, in part, be owing to the lack of a solid scientific evidence base, particularly for the smallest and most immature infants. However, there is also an impression that the dispensing and dosing of phototherapy may have been less rigorously controlled than other types of therapy in the NICU. The latter could perhaps be explained on the background of the widespread idea that phototherapy is harmless.

Maisels recalculated the data from the Collaborative Phototherapy Trial,[7,8] and found a relative risk (RR) of death of 1.49 (95% confidence interval [CI], 0.93–2.40) in infants who received phototherapy versus controls.[9] In the original publication, the differences were discounted because they did not reach statistical significance.[8] Recently, Tyson and colleagues[10] published a reanalysis of the data from the National Institute of Child Health and Development Neonatal Research Network study on 'aggressive' versus 'conservative' phototherapy. Using a Bayesian analysis approach, they found that the risk of death was significantly increased (RR, 1.19; 95% CI, 1.01–1.39) in the 501 to 750 g birthweight mechanically ventilated subgroup treated with 'aggressive' phototherapy.

Thus, it is clear that despite more than 50 years of practical use of phototherapy, we still have more to learn. This paper reviews the state of our knowledge regarding the biology of bilirubin photoisomers, the phototherapy products that are thought to be responsible for the effects of this therapeutic modality. The physics and physiology of phototherapy will be only briefly mentioned here for context and for more details (See Lamola AA: A pharmacological view of phototherapy, in this issue).

BILIRUBIN TOXICITY

We treat neonatal hyperbilirubinemia because bilirubin is toxic to the brain. These toxic effects can range from transitory (bilirubin-induced neurologic dysfunction) to the devastating and chronic (kernicterus, chronic bilirubin encephalopathy), and not infrequently also in death.[11] Efforts to discover the 'basic mechanisms' of bilirubin neurotoxicity started more than one-half of a century ago and are ongoing. For details, the interested reader is referred to recent reviews.[11,12] Briefly, bilirubin seems to be toxic in a large number of in vitro systems in which it has been tested. It has been suggested that this could be a false lead, as bilirubin seems to share many of the characteristics of so-called promiscuous inhibitors, compounds that have apparent effects in vitro, but fail to show any such effects when tested in vivo.[13] This author has suggested that such widespread inhibitory effects might also be understood in terms of interference with a basic, common regulatory mechanism such as protein phosphorylation.[12]

The majority of in vitro studies have been performed with bilirubin-IXα (*Z,Z*), the predominant in vivo isomeric form of bilirubin. The lipophilicity of this isomer enables it to cross membranes, and thus gain entry into cells as well as organs. Important in the