ELSEVIER

SEMINARS IN PERINATOLOGY

The Role of Phototherapy in the Crash-Cart Approach to Extreme Neonatal Jaundice

Thor Willy Ruud Hansen, MD, PhD, MHA*,†

Extreme neonatal jaundice occurs infrequently but carries a high risk of permanent sequelae (kernicterus) when it does. Rapid therapeutic intervention has the potential to reduce this risk in some infants. Several case reports of infants with acute intermediate to advanced bilirubin encephalopathy shows that reversal may be possible. Phototherapy can be instituted at the flip of a switch, whereas other therapeutic measures necessarily involve delays. Therefore, high-intensity phototherapy must be regarded as an emergency measure in infants presenting with extreme jaundice and even more so in the presence of neurological symptoms. The principal and well-described effect of phototherapy involves conversion of bilirubin IXα (*z, z*) to more polar isomers, which are excreted in bile and urine. When care is taken to maximize the spectral power of phototherapy lights, and whenever possible with measures added to reduce the enterohepatic circulation of bilirubin, very rapid reductions in total serum bilirubin levels are possible. A hypothesis has been advanced that conversion of bilirubin to more polar photoisomers, which can reach relative concentrations of 20%-25% of total serum bilirubin within 1-2 hours, might have a direct neuroprotective effect. This theory posits that because polar molecules generally require a transporter to cross the blood–brain barrier, bilirubin photoisomers should be less prone to enter the brain. Although this theory has some support in in vitro toxicity studies, the evidence is controversial. Until further experimental support can be gained, photoconversion of bilirubin does not constitute a viable argument against instituting further measures against bilirubin neurotoxicity, such as intravenous immune globulin (when indicated) and exchange transfusion. Conversely, neither is the state of evidence an argument against immediate and effective phototherapy in the medical emergency of extreme neonatal jaundice.

Semin Perinatol 35:171-174 © 2011 Elsevier Inc. All rights reserved.

KEYWORDS acute bilirubin encephalopathy, bilirubin, bilirubin isomers, kernicterus, neonatal jaundice, phototherapy

Extreme neonatal jaundice continues to occur despite measures to identify infants at risk before they are discharged from the birth hospital.[1] The incidence of extreme jaundice in neonates has been studied in several countries, and estimates have ranged from 7.1/100,000 live births to 150/100,000.[1–4] Kernicterus, the often devastating sequelae of inadequately treated neonatal jaundice, also still happens.[5–7] Until recently it has been believed that acute bilirubin encephalopathy, when it has reached the intermediate to advanced stages, is irreversible.[8] However, recent case series suggest that complete or at least very significant reversal of toxicity may be possible.[9–11] Although the data do not allow for an estimate of the proportion of such cases that may be reversed, there is evidence to suggest that the likelihood of a successful outcome depends on rapid and effective institution of treatment.[10] With this background, the need for a "crash-cart approach" to the management of infants with extreme neonatal jaundice has been argued.[12,13] The purpose herein is to review the role of phototherapy and photoisomerization of bilirubin in a crash-cart approach.

The Mechanism of Phototherapy

The beneficial effect of light on neonatal jaundice was discovered by an astute English nurse who noted that the skin of jaundiced infants who had been exposed to bright daylight

*Department of Neonatology, Women's and Children's Division, Oslo University Hospital–Rikshospitalet, Oslo, Norway.

†Institute for Clinical Medicine, Faculty of Med, University of Oslo, Oslo, Norway.

Address reprint requests to Professor Thor Willy Ruud Hansen, MD, PhD, MHA, Kvinne-og Barneklinikken, Oslo Universitetssykehus, Rikshospitalet, N-0027 Oslo, Norway. E-mail: t.w.r.hansen@medisin.uio.no

0146-0005/11/$-see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1053/j.semperi.2011.02.012

appeared less yellow than skin that had been protected by diapers or clothing[14,15] Subsequent trials documented the effect of this, largely innocuous, treatment as far as lowering serum bilirubin levels.[16]

The bleaching effect of light on jaundiced skin explains why transcutaneous measurement of bilirubin does not correlate well with serum bilirubin values in infants undergoing phototherapy, as there will be an unpredictable gradient between skin and serum bilirubin.[17] The relative importance of skin bleaching in the therapeutic effect of phototherapy has long been thought to be considerable and was manifested by the common practice of turning infants in phototherapy over between supine and prone positions at intervals to irradiate skin that had not been exposed to the lights.[18] Recent data from Donneborg et al[19] show that turning the infant over does not significantly impact on the effect of phototherapy and suggest that bilirubin circulating in skin capillaries may be a more important target for photoconversion. This also seems compatible with recent data from our group, which show that significant conversion of bilirubin to photoisomers can be measured in serum within a few minutes of starting phototherapy.[20] Indeed, significant photoconversion of serum and tissue bilirubin happens long before changes in total serum bilirubin (TSB) are detectable.[20,21]

When exposed to light, a fraction of bilirubin in tissues and blood undergoes photochemical conversion reactions occurring at different rates and resulting in several different products. Configurational isomerization results in Z,E and E,Z isomers; is reversible; and is much faster than structural isomerization, which is irreversible and results in lumirubin (see Maisels and McDonagh[21] for a review). Photooxidation was initially thought to be the main mechanism for phototherapy. This reaction occurs much more slowly than the other 2, and is thought to be less important than configurational and structural isomerization.[22] Elimination of bilirubin photoproducts occurs both in bile and in urine, and depends both on the rates of formation as well as the rates of clearance of these products. It is important to remember that reduced ability to conjugate and excrete bilirubin are key factors in the mechanisms of jaundice in the neonate, and that phototherapy is effective because it bypasses these relative defects.

Bilirubin absorbs most light at 460 nm in the blue region of the spectrum. So-called "special blue," turquoise, and green lights are more effective than white/daylight lamps.[23-26] Considering that longer wavelengths penetrate more deeply into the skin, these data seem compatible with the concept that conversion of bilirubin circulating in skin capillaries is very important in the clinical effect of phototherapy.[19]

Clinical Use of Phototherapy

The clinical effect of phototherapy, in addition to wavelength, also depends on the energy of the light, also called irradiance, and the number of molecules which is concurrently irradiated. The number of exposed bilirubin molecules obviously depends on the TSB level, ie, the greater the TSB the more bilirubin molecules will be present in skin as well as in circulating blood.[27] However, it also follows that the number of exposed bilirubin molecules in skin and capillary circulation will depend on the size of the irradiated skin area. Indeed, the product of irradiance and irradiated area of skin, known as spectral power, is a key concept in effective phototherapy.

Irradiance is typically reported in watts per square meter or in microwatts per square cm per nm over a certain wavelength band. Unfortunately, the devices for measuring irradiance are not standardized. Conventional daylight phototherapy lamps can be expected to deliver an irradiance of approximately 8-10 $\mu W/cm^2/nm$, although this may be improved by bringing the light source closer to the infant (no more than 20 cm away) and using bright reflecting surfaces in and around the bed.[28] With special blue fluorescent lamps irradiance levels may reach 30-40 $\mu W/cm^2/nm$.[29] The American Academy of Pediatrics defines intensive phototherapy as a spectral irradiance of at least 30 $\mu W/cm^2/nm$ delivered to as much of the infant's body-surface area as possible.[30]

The effect of phototherapy is typically measured in reduction of the infant's TSB level. The effect you can anticipate will depend on several factors. First, if phototherapy is initiated during the first 3-4 days of life when TSB levels would normally be expected to increase, a satisfactory effect of phototherapy might be a leveling off of TSB levels, or a reduced rate of increase. Thus, an absolute reduction of TSB levels may not always be achievable during this phase. If phototherapy is started after this period, effective phototherapy should lead to a measurable reduction of TSB within 4-6 hours.[29] In extreme neonatal jaundice (TSB levels >30 mg/dL [=513 μmol/L]), we have previously documented reductions up to 10 mg/dL (=171 μmol/L) during the first 2 hours.[31] Others have shown a decrement of TSB values of 30-40% over the first 24 hours, with the most pronounced decline occurring in the first 4-6 hours.[32] Even greater reductions have recently been shown in patients with extreme jaundice and acute intermediate to advanced stage bilirubin encephalopathy where phototherapy was used in conjunction with intravenous immune globulin and/or exchange transfusion.[11]

Thus, in infants treated for extreme jaundice key points are to maximize irradiance and spectral power, in addition to reducing the enterohepatic circulation of bilirubin because some of the isomer excretion occurs in bile. Irradiance is maximized by bringing the lights (except quartz lights!) as close to the infant as possible—no more than 10-20 cm distance between the infant's skin and the phototherapy lights. Light bulbs should be as fresh as possible, and any optical filters in the unit should be cleaned regularly. Spectral power is optimized by exposing as much skin as possible, exceptions being the need for protective covering of the eyes and, if absolutely necessary, diapers cut down to minimal working size. Reflecting white linen or other material inside the basinette or incubator and along the sides of the phototherapy unit will increase irradiance.[28] Whether double or triple phototherapy[33] will help further has not been tested using modern, high-energy phototherapy units, although such deployment apparently continues to occur. The risk–benefit ratio of this approach in an infant threatened by neurotoxicity, at least until further data accrue, appears to be extremely low.