CHAPTER 13

PHOTOTHERAPY OF NEONATAL JAUNDICE

Neonatal jaundice is the most common problem encountered in newborns. 50% of term (> 37 weeks of gestation) and 80% of preterm babies are jaundiced within the first week. It is the most common cause for hospital admission in the first week of life, especially since the advent of early postpartum discharge programs. Unbound serum *bilirubin* (BR) or *hyperbilirubinemia* is the usual cause of neonatal jaundice. BR is a breakdown product of blood heme. Circulating free BR can enter almost all tissues of the body and is highly neurotoxic. Hyperbilirubinemia develops when the BR production exceeds the infant's capacity for its elimination. Normal plasma concentrations of BR are about 1.5 - 2.0 mg/dL (1mg/dL corresponds to 17 μmol/L). Jaundice is evident at 5.0 - 6.0 mg/dL. Total serum bilirubin (TSB) levels exceeding 10 mg/mL can induce delayed neurological damage evident in early childhood. *Kernicterus* is a severe form of hyperbilirubinemia in which very high serum BR concentrations induce deafness, cerebral palsy, or death. Hemolytic disease of the newborn is the classic cause of pathologic hyperbilirubinemia originating from maternal-fetal blood group incompatibility, genetic deficiencies in red blood cell metabolism, infection, and drugs. Total blood exchange was the only treatment for kernicterus prior to discovery of the phototherapy (PHB) in the late 1950's.[1] The phototherapy of neonatal jaundice originated from observations of J. Ward, a nursing sister who supervised a premature baby ward in Essex, U.K.. Sister Ward observed that the skin of jaundiced infants became bleached when exposed to sunlight. Controlled testing by Dr. R. J. Cremer and his associates demonstrated that sunlight reduces the serum BR levels in the infants. Cremer designed an irradiator consisting of eight blue fluorescent lamps and reported the successful reduction of both jaundice and unbound serum bilirubin. PHB is not without side effects, notwithstanding the widespread notion that visible light can only be beneficial. The eyes of the infant must be completely protected from the phototherapy light. The short-term adverse effects of PHB include temporary retardation of growth, increased insensible water loss, immune suppression, transient alterations in blood chemistry, and alteration of biologic rhythms. Clinical experience has not shown evidence of long-term adverse effects.

13.1 METABOLISM OF BILIRUBIN

The turnover rate of red blood cells is approximately three million cells per second. Humans utilize a multi-organ system for elimination of the excess heme (Figure 13.1). The membrane-bound enzyme heme oxygenase in the spleen opens the heme ring and removes the bridging α-carbon as CO, leading to the blue-green bile pigment biliverdin (BV) which has no known function (Figure 13.2). Biliverdin is reduced to BR by the enzyme biliverdin reductase. BR is insoluble
in water at physiologic pH and has an exceptionally high binding affinity for serum albumin (ALB). The BR-ALB complex cannot cross the blood-brain barrier. Excretion of the BR-ALB complex is mediated in the liver by the enzyme uridine diphosphate glucuronyl transferase (UDPGT), which conjugates BR with one or two molecules of glucouronic acid to form the mono- and di-glucuronides. The conjugated BR is excreted into the bile canaliculi of the liver, followed by transfer to the gall bladder and then to the intestine where it is excreted in feces. A small amount of BR is transferred to the kidneys and excreted in urine. Hyperbilirubinemia results when the formation and/or excretion of BR glucouronides becomes impaired. This conditions occurs most frequently in premature and newborn infants until UDPGT activity in the liver increases.

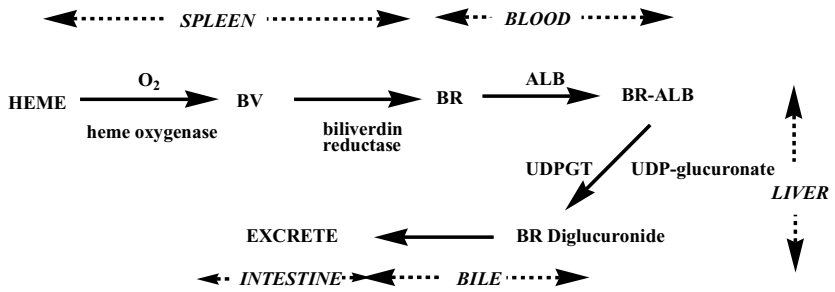


Figure 13.1 Simplified biochemical pathway for degradation of heme

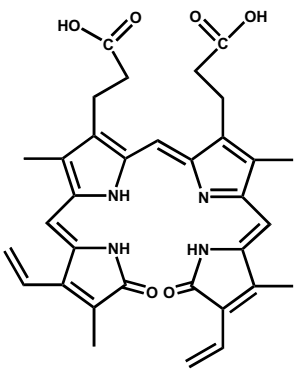
13.2 ACTION MECHANISM OF PHB

The interaction of light with BR is believed to take place mostly in extravascular tissues within 1 mm of the skin surface. Early workers postulated that PHB involves an *intra*molecular photosensitization, in which light absorption by BR generates $^1O_2$ which then oxidizes BR to biliverden. However, photooxidation products account for only a small fraction of the BR eliminated

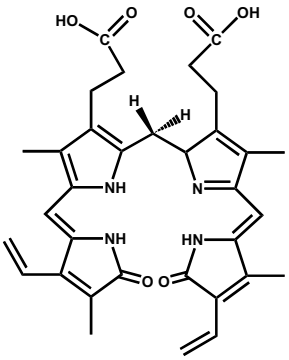
by PHB. There is now ample evidence that BR elimination is initiated primarily by anaerobic *photoisomerization* reactions. Two types of photoisomers have been identified. Four "configurational" photoisomers are formed *in vitro* by rotations of the BR molecule around the C=C bonds at C-4 and C-15, which are stabilized by *intra*molecular hydrogen bonds. Of these, only the 4Z,15E-photoisomer (referred to as *photobilirubin*) appears in infant's blood after phototherapy (Figure 13.2).[2] The photochemical conversion of bilirubin to photobilirubin is efficient *in vitro* with an initial quantum efficiency about 0.2 for blue light. However, this photoisomer also absorbs blue light and continuous irradiation establishes a *photoequilibrium* at a low level of conversion. Consequently, photobilirubin accumulates in blood of jaundiced infants and only a small amount is excreted BR binding to ALB does not inhibit the formation of photobilirubin. The other type of photoproducts are "structural" isomers referred to as *lumirubin* (Figure 13.2). The photochemical production of lumirubin is the order of 20-fold less efficient than the photobilirubin. However, this process is irreversible and provides the major pathway of BR removal. PHB also generates a low yield of colorless photooxidation products which are eliminated *via* the kidneys. According to the present model, light absorption in the skin of the infant converts unbound serum BR to albumin-bound photoisomers which are carried to the liver and eliminated in the intestine. BR photooxidation products are carried to the kidney and eliminated in urine.

13.3 PHB LIGHT SOURCES

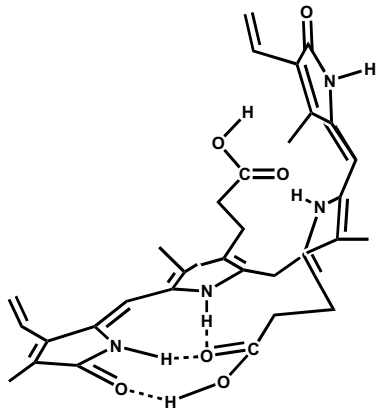
The absorption spectrum of BR in a nonpolar solvent consists of a broad band extending from 350 nm - 500 nm peaking near 455 nm (Figure 13.3). Accordingly, PHB light sources are designed to emit the blue light most strongly absorbed by BR. The conventional light sources for PHB are fluorescent lamps providing the order of 1 mW/m^2 in the blue spectral region. In an early controlled study of Dr. T. R. C. Sisson, initiation of phototherapy in 2 - 3 day old infants with "blue" (B) fluorescent lamps led to a decrease of serum BR from an average of 10 mg/dL to 7 mg/dL after 1 - 2 days of treatment. The untreated control group reached BR levels of 13 mg/dL after 4 - 5 days of age, which decreased to 9 mg/dL after 3 - 4 additional days. Different types of fluorescent lamps have been used in phototherapy units, all of which have appreciable output from 420 to 470 nm.



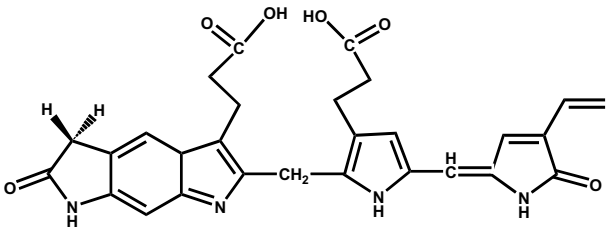
Biliverdin



Bilirubin



Photobilirubin



Mirubin

Figure 13.2 Chemical structure of bile pigments

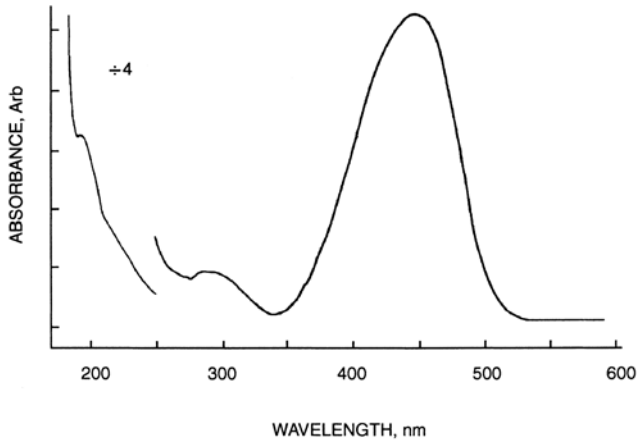


Figure 13.3 Absorption spectrum of bilirubin in acetonitrile

The more common types are the "daylight" (DA) lamp with a broad emission from 400- 650 nm, "standard blue" (B) with a narrower band peaking near 450 nm, and "special blue" (BB) which is more intense than "standard blue" with a narrower bandwidth. Table 13.1 summarizes radiometry measurements of Pratesi *et al.* for several types of fluorescent lamps. The last column is a relative photophysical efficiency parameter, calculated by the present author, defined as $E_{max}\,\Delta\lambda\,\varepsilon_{BR}$, where E_{max} is the peak irradiance of the lamp, $\Delta\lambda$ is the spectral width of the emission, and ε_{BR} is the extinction coefficient of BR at the peak wavelength. This parameter suggests that either the "standard blue" (Type B) or "special blue" (BB) fluorescent lamps should be the most efficient light sources of this group. This photophysical calculation does not include the higher absorption of shorter wavelengths by the epidermis and the dependence of the photochemical quantum yields on wavelength. Alternative blanket-type irradiators have been available for about 10 years. In one type of arrangement, a flexible light-emitting panel is wrapped around the infant. A QTH lamp is used as the light source, delivered by multiple optical fibers to a phosphor emitting blue light. Representative systems include the Ohmeda BiliBlanket® and the Heathdyne Wallaby®. A different approach employs an illuminated blanket that delivers the therapeutic light to the infant's back, for example the Medela Bilibed®. These devices have the advantages that infants can be nursed close to their parents without the need for eye protection. A recent evaluation of 24 comparative studies does not indicate a clear superiority of either the conventional overhead lamps or the newer optical fiber devices, although combinations of the two modalities were more effective than the overhead lamp

phototherapy alone[3].

Table 13.1 Properties of fluorescent lamps used for PHB

Lamp Type	λ_{max} [a] (nm)	$\Delta\lambda$ [b] (nm)	E_{max} [c] (rel)	ε [d] (rel)	$E_{max}\,\Delta\lambda\,\varepsilon$ [e] (rel)
Violet Blue	419	33	1.46	0.81	39
Special Blue (BB)	440	34	1.01	0.97	33
Blue (B)	452	54	1.00	0.99	54
Green (G)	528	38	0.72	0.02	0.5
Daylight (DL)	667	40	0.18	0.10	0.7[f]

[a] Wavelength of maximum emission; [b] full-width of lamp emission at half-peak irradiance; [c] peak irradiance; [d] bilirubin extinction coefficient; [e] photo-physical efficiency factor, [f] calculated for 455 nm.

13.4 CLINICAL ASPECTS OF PHB

The basic objective of PHB for healthy term newborns is to ensure that the TSB levels after 24 hours do not attain pathologic levels. There is no clear evidence for the superiority of different light sources and treatment protocols. Clinical studies comparing intermittent with continuous phototherapy have produced conflicting results. The clinical guidelines for management of non-pathologic hyperbilirubinemia recommended by the American Academy of Pediatrics are based on the belief that therapeutic intervention may carry significant risk relative to the uncertain risk of hyperbilirubinemia in this population[4]. The preliminary diagnosis requires visual observation of jaundice, determination of TSB levels, and acquisition of information that might indicate other causes of hemolytic disease. Recommendations for application of PHB depend on both the age of the infant and the TSB level. At 24 - 48 hours PHB should be considered for TSB > 12 mg/dL and is indicated for TSB in the range from 15 to 20 mg/dL. Higher levels of TSB require intensive phototherapy and possibly exchange transfusion. Term infants who are clinically jaundiced at < 24 hours old are not considered healthy and require further evaluation. Additional details are available in the pediatric literature.

NOTES

1. There is no generally accepted abbreviation for the phototherapy of hyperbilirubinemia. PHB is used in this chapter.

2. The molecular structures employ the standard convention in which obvious C-H bonds are not shown and methyl and vinyl groups are indicated by single and double lines, respectively.

3. Tudehope D, Crawshaw A. Fibreoptic versus conventional phototherapy for treatment of neonatal jaundice. *J Paediatr Child Health*. Feb 1995;31(1):6-7.

4. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. American Academy of Pediatrics. Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia. *Pediatrics*. 1994 Oct;94(4 Pt 1):558-65.