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Mechanism of Phototherapy on Hyperbilirubinemiaand clinical applications

S. Sunpavat

บทความพิเศษ

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Suwimol Sanpavat*

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The mechanism of phototherapy in reducing bilirubin level was thought to be due to photo-oxidation which involved singlet oxygen and caused the disintegration of the molecule, resulting in several colorless water-soluble products that could be excreted in the urine. It has been discovered recently that the major pathway is photoisomerization, yielding photoisomers which have the same molecular formula but the atoms are arranged differently. The photoisomers which can be excreted without conjugation into the bile, is unstable and converted to the parent bilirubin rapidly.

Clinically phototherapy has been used to prevent hyperbilirubinemia in very low birthweight high-risk infants and will reduce the frequency of exchange tranfusion in ABO and Rh hemolytic disease. Once started, phototherapy is to be continued until the level of bilirubin is less than half of that indicated for exchange transfusion. The phototherapy unit comprises of 8 to 10 fluorescent lamps from which the minimal energy output at the infant's skin should be 4 uw/cm^2/nm to achieve the desirable effect. The important side effect of phototherapy is increased insensible and intestinal water loss, so that extra fluid should be given. Although retinal damage is not proven in human infant, covering the infant's eyes during phototherapy is recommended.

* Department of Pediatrics, Faculty of Medicine, Chulalongkorn University.

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การรักษาภาวะตัวเหลืองในเด็กหลังคลอด โดยวิธีฉายแสงเป็นวิธีที่ใช้กันแพร่หลาย กลไกในการลดระดับบิลิรูบินจากการฉายแสงเกิดได้ 2 วิธีแรก คือ ***Photo-oxidation*** *หรือ* ***Photo-degradation*** *เกิดในภาวะที่อ็อกซิเจนทำปฏิกิริยากับโมเลกุลของบิลิรูบินและแสงทำให้โมเลกุลแตกออกเป็นสารที่ไม่มีสีและถูกขับถ่ายออกทางปัสสาวะ วิธีนี้เกิดเป็นส่วนน้อย วิธีที่สองเป็นกลไกหลัก คือ* ***Photoisomerization*** *เกิดจากการที่อะตอมในโมเลกุลของบิลิรูบินหมุนเปลี่ยนทิศทางทำให้รูปร่างเปลี่ยนไปจากเดิม เกิดสาร* ***Photoisomers*** *ซึ่งมีคุณสมบัติพิเศษคือ ร่างกายขับถ่ายออกทางน้ำดีได้โดยไม่ต้อง* ***conjugate*** *ในตับ* ***Photoisomers*** *เป็นสารที่ไม่คงตัว สามารถเปลี่ยนกลับไปอยู่ในสภาวะเดิมได้อย่างรวดเร็วและถูกดูดซึมกลับเข้าสู่กระแสโลหิต ฉะนั้นถึงแม้ปฏิกิริยานี้จะเกิดขึ้นทันทีเมื่อเด็กถูกแสงแต่ก็ต้องใช้เวลานานหลายชั่วโมงกว่าระดับบิลิรูบินในเลือดจะลดลงอย่างชัดเจน*

ในทางคลินิก ใช้การฉายแสงรักษาเด็กทารกที่มีภาวะเหลือง โดยป้องกันมิให้ระดับบิลิรูบินสูงจนเกินไปในเด็กน้ำหนักน้อยที่มีความเสี่ยงสูง ในรายที่เหลืองจากหมู่เลือดที่แตกต่างกันของมารดาการฉายแสงจะช่วยลดจำนวนที่ต้องทำการถ่ายเปลี่ยนเลือดให้น้อยครั้งลง ในการรักษาควรให้แสงจนระดับบิลิรูบินลดลงต่ำกว่าครึ่งหนึ่งของระดับที่ต้องทำการถ่ายเปลี่ยนเลือด เครื่องฉายแสงส่วนใหญ่ประกอบด้วยหลอดไฟ 8-10 หลอด ส่วนมากนิยมใช้ไฟนีออนสีขาว ซึ่งต้องให้พลังงานแสงที่ผิวหนังอย่างน้อย 4 ไมโครวัตต์/ตาราง ซม./แนนโนมิเตอร์ ผลข้างเคียงที่สำคัญ คือ การเสียน้ำจากร่างกายทาง ***insensible water loss*** *และทางลำไส้มากกว่าปกติ จึงจำเป็นต้องให้สารน้ำทดแทนให้เพียงพอ ในสัตว์ทดลองพบมีการเสื่อมสภาพของเรตินา ฉะนั้นจึงควรปิดตาเด็กทารกขณะฉายแสง*

Bilirubin is the breakdown product of heme. In the newborn infant, 75% of the daily bilirubin production comes from the turnover of circulating red blood cells. The other 25% are from the ineffective erythropoiesis, the destruction of immature red blood cells, the nonhemoglobin hemeproteins and the free-heme mostley from the liver[1] Bilirubin which is lipophilic is then taken up by the hepatocyte, conjugated into the water-soluble form or direct-reacting bilirubin and excreted in the bile.

Due to the inadequacy to cope with the load of bilirubin being produced, the unconjugated bilirubin casts a major problem in the neonatal period. It accumulates in the circulation, extra-vascular tissue, and most importantly, across the blood-brain barrier, staining the central nervous system and causing bilirubin encephalopathy. Phototherapy was reported to effectively reduce hyperbilirubinemia by Cremer and associates in 1958[2] Since then it has been widely practiced in the neonatal unit, although the exact mechanism of action in reducing bilirubin has not been clearly understood until recently. The purpose of this paper is to review the chemical structure of bilirubin and the action of phototherapy in the reduction of bilirubin in the neonates.

The chemical structure

Bilirubin is derived from the cleavage at the alpha methene bridge in the heme ring of ferroprotoporphyrin IX[1]. The product formed, bilirubin IXα (ZZ) isomer, is thought to be the main component of natural bilirubin[3]. Other isomers derived from breaking at the β, γ and δ positions are found in small amounts.[3]

Bilirubin IX O (ZZ) consists of two dipyrroles (A, B and C, D) connected by a central methylene bridge. Two propionic acid side groups are attached to the central pyrrole rings B and C. The commonly written linear form is shown in Fig 1[4]

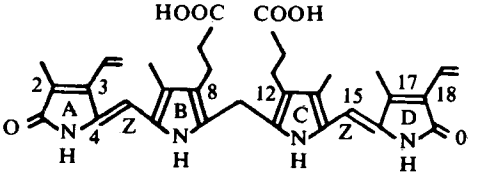
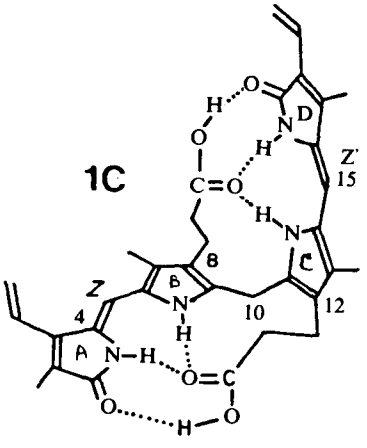


Figure 1. Chemical structure of bilirubin IX α (ZZ)

Actually, the molecule is flexible and can assume various shapes of different stability. The two dimensional structural diagram is similar to a bent paper clip[5] (Fig 2).



Figrue 2. Structural diagramme of the prefered shape of bilirubin.

In this involuted structure, the propionic acid groups of ring B and C are linked to the nitrogen of the opposite pyrrole rings (broken lines) by an intramolecular hydrogen-bond[4]. So the hydrophilic polar COOH and NH groups are unavailable for affinity with other polar groups, thus leaving the bilirubin IX ∝ (ZZ) hydrophobic and insoluble in water.

Phototherapy

For the light to exert any effect on any molecule, it has to be absorbed. The light of wavelength between 440-470 nanometers was discovered to be most effective in reducing serum bilirubin concentration[1]. Absorbing a quantum of light, the bilirubin molecule becomes activated and is in the high-energy excited state which does not remain for long. It then undergoes some reactions to form photoproducts. Photooxidation and photoisomerization appear to be the two types of reaction taking place[5]

1. Photooxidation or photodegradation An observed increase of propentdyopent adducts in the urine after phototherapy[6] suggests a photodegradation pathway. Its mechanism was postulated as the formation of oxidative bilirubin by photosensitization involving singlet oxygen[7]. This pathway leads to the bleaching and disintegration of the molecule, yielding several small polar, colorless and water soluble products that can be easily excreted in the urine.[8] The role of this pathway is probably small[5]. The main products are as shown in Fig. 3

2. Photoisomerization This reaction which is the major pathway, is faster than that of photo-oxidation. A substance undergoing isomerization keeps the same molecular formula but differ in the way its constituent atoms are arranged. Such compounds also differ in their chemical and physical properties[9]

One of the photoismoerization is called geometric or configurational isomerization. One of the pyrrole rings rotates 180° about the double bond attaching it to its neighbour[10] (Fig 4). This transformation is described as Z — E isomerization

Because bilirubin IX ∝ (ZZ) contains two unsymmetrically substituted double bonds at C-4 C-5 and C-15 C-16, four

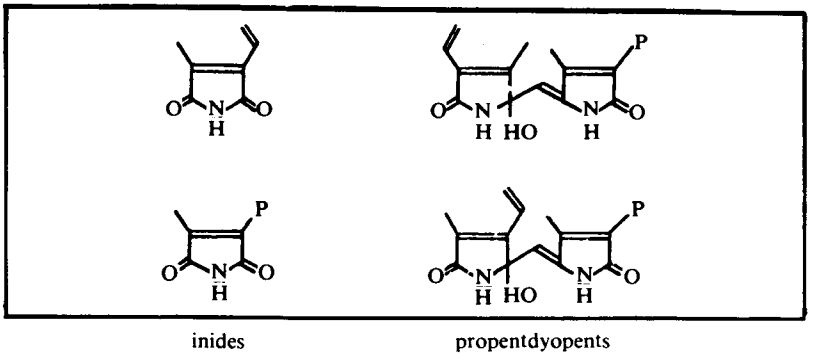


Figure 3. Major photo-oxidation products of bilirubin

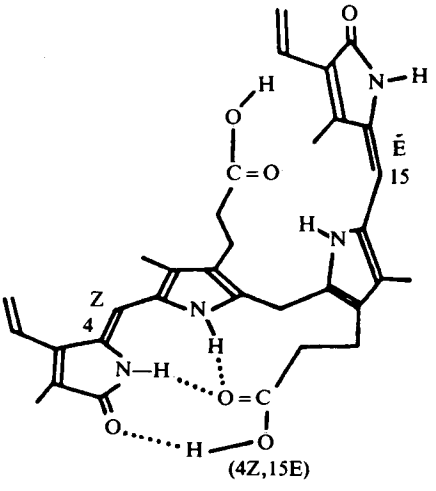


Figure 4. Z — E Carbon-Carbon double bond configurational isomerization of bilirubin in human.[5]

geometric isomers of bilirubin are possible, the (4Z, 15Z), (4Z, 15E), (4E, 15Z) and the (4E, 15E)[11] (Fig 5).

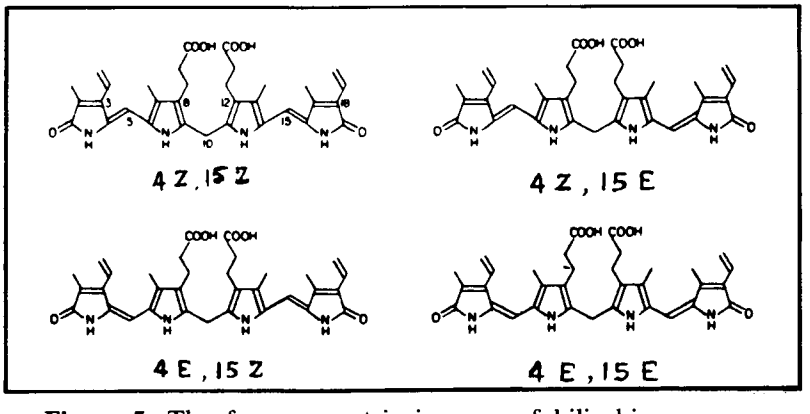
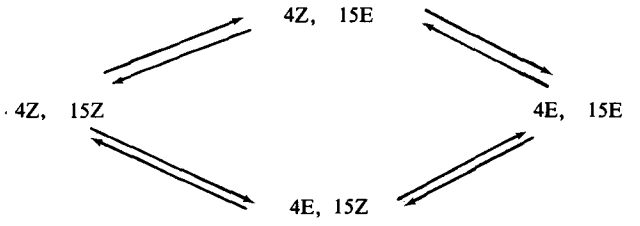
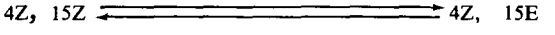


Figure 5. The four geometric isomers of bilirubin.

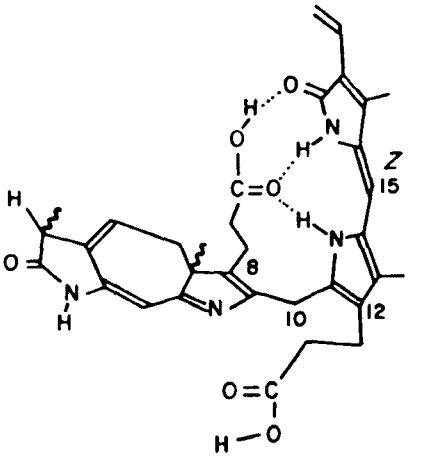
These photoisomerization reactions are all reversible and, a photoequilibrium in vitro can be written as[12]



In dynamic system such as the human body, the photoismoers may not remain long enough for complete photoequilibration to occur,[11] and bilirubin bound to human serum albumin yields only the 4Z, 15E isomer[12]. Therefore, the geometric photoisomerization of bilirubin bound to human albumin can be simplified as[11]

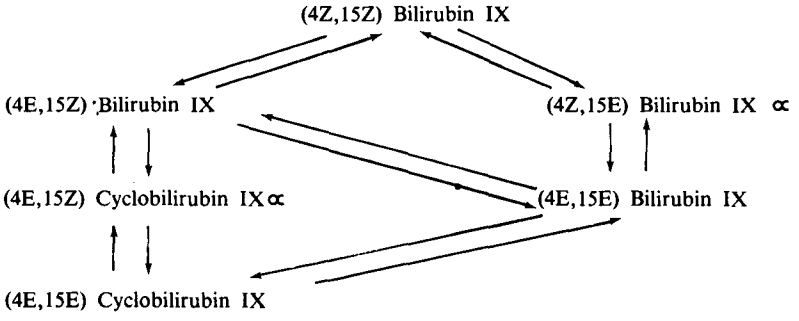


Another photoismoer is called a structural isomer. The side chain double bond at C 3 of one ring forms a new bond with an adjacent pyrrole ring giving an isomer called lumirubin[13] or EZ cyclobilirubin[14-17] (Fig. 6)



Figrue 6. Intramolecular cyclization of the endovinyl group of E isomer into EZ cyclobilirubin.

On prolonged irradiation, another isomer is formed in vitro, presumably 4E, 15E cyclobilirubin.[16,17] The interrelationship of bilirubin IX α and its products in vitro was proposed as in the scheme.[16,17]



In a jaundiced neonate during phototherapy, the serum concentration of photobilirubin IX (ZE, EZ) increases significantly.[18] It is then excreted by the liver without conjugation and reverts spontaneously into natural bilirubin IX (ZZ) in the bile. The rate of reversion at 37° C in Gunn rat was very rapid; its half-life was 6.2 minutes.[15]

The rate of formation of lumirubin or (EZ) cyclobilirubin is slow in vivo,[5,11] but it is excreted more rapidly when compared to the photobilirubin (EZ, ZE) The mean values of half life for the appearance of (EZ) cyclobilirubin and photobilirubin (EZ, ZE) in bile of the Gunn rat were 4.3 and 29.8 minutes respectively.[15] A high concentration of (EZ) cyclobilirubin is therefore detected in the bile[18] but not observed in the circulation.

The result of photoisomerization is the exposure of the polar N and O groups so that the molecule would be expected to hydrogen-bond to water, become more soluble and excretable in bile without conjugation.[5]

Clinical application of phototherapy

It is well documented that phototherapy is effective in reducing bilirubin in the jaundiced newborn infant. In ABO and Rh-hemolytic diseases, phototherapy will reduce the frequency, although not replace the need of exchange transfusion[19] It is used for the prevention of hyperbilirubinemia in the very low birth-weight high-risk infant[20] Once started, it is to be continued until the serum bilirubin falls to level less than half of that normally indicated for exchange tranfusion. After discontinuation a rebound of one to two mg/dl of bilirubin in nonhemolysis is expected. As light causes the bleaching of skin, the measurement of serum bilirubin level is more reliable than clinical assesment of jaundiced skin after the exposure[21].

The effectiveness of phototherapy depends largely on the irradiance at the infant's skin. The irradiance or energy output of the lamps is expressed as the quantity of radiant power or energy watt/cm^2 over a particular wavelength interval. A Minimum irradiance of 4 uw/cm^2/nm is necessary for phototherapy to achieve the desirable effect[22].

Various types of fluorescent light with different spectral emission have been used :- day light, cool white, blue and special blue. Day light and cool white lamps have a spectral range of 380-700 nm with the spectral peak between 550-600 nm. Blue and special blue lamps have a peak between 420-480 nm[1]. Since bilirubin absorbs light maximally in the range of 420-500 nm[23], blue and special blue lamps appear to be more effective in reducing bilirubin concentration than the day light and cool white ones. However, blue light causes the infant to look cyanotic and some of the personnels to become dizzy and nauseated, thus the broad-spectrum light has gained more popularity.

The standard phototherapy unit consists of banks of 8 or 10 fluorescent lamps, placed approximately 12 to 16 inches above the unclothed infant. A shield of plexiglass placed between the lamps and the infant will absorb the ultraviolet light emitted by the fluorescent lamps and guard against injury from lamp explosion[23].

Possible side effects and complications

1. Retinal damage. Study in animals demonstrated retinal degeneration after exposure to high intensity light. Although this is uncertain in human infant, it is reconmended that the infant's eyes be covered during phototherapy[23].

2. Platelet. Phototherapy increases platelet turn-over rate, resulting in low platelet count. No clinical bleeding has been noted[1].

3. Riboflavin. Riboflavin is a light-sensitive substance, and phototherapy may cause photodegradation of this vitamin. A deficiency of riboflavin has been reported[24].

4. Increased insensible and intestinal water loss. Extrafluid should be considered for infants undergoing phototherapy[1]

5. The Bronze baby syndrome. Infants who have direct treacting bilirubinemia developed a gray-brown discolouration of the skin, serum and urine after being placed under the light. The nature of the bronze pigment is unknow. Most of the infants recover after discontinuing the light.

Other possible dangers are overheating of the infant and electric shock from electrical leakage or poorly grounded equipment. Follow-up study has not shown any significant difference on growth of the infants receiving phototherapy.

Summary

The mechanism of phototherapy was initially thought to be due to photo-oxidation with the formation of oxidative bilirubin derivatives, which were colorless and excreted in the urine. However, this did not correlate with the appearance of a large amount of unconjugated bilirubin excreted mostly in the bile and to a lesser degree in the urine in Gunn rats animal model[25] and newborn infants[26] after phototherapy. It has been proved recently that not photooxidation but photoismoerization is the prominent reaction when bilirubin absorbs light. These unstable, reversible isomers are the same color as the natural bilirubin, but more polar, hydrophilic and nontoxic. They are formed near the surface of the skin and transported in the plasma to the liver, where they are excreted in the bile without conjugation.

Of the photoproducts, photobilirubin IX α (ZE), a geometric photoisomer is formed most rapidly, but its rate of excretion is slow, so it accumulates in the circulation. This substance may constitute about 10-20% of the total plasma bilirubin.[11] Its reversion in bile to natural

bilirubin IX ∝ (ZZ), which is then reabsorbed through the enterohepatic circulation[27], may, to some extent, account for the slow decline of the serum bilirubin during phototherapy.

On the other hand, the formation of (EZ) cyclobilirubin or lumirubin, a natural isomer, is slow, but cleared from the circulation rapidly so that a considerable amount is found in the bile but not in the blood.

The physiologic response to light is fast, the process begins as soon as the infant is exposed to the light, but the net effect is slow, since it takes hours to lower the serum bilirubin level.

Phototherapy is used for prevention of hyperbilirubinemia in very low birthweight high-risk infants. It also reduces the frequency of exchange transfusion in ABO & Rh hemolytic diseases. The important side effect is the increased insensible and intestinal water losses in infants and retinal degeneration in experimental animals.

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