

PHOTOTHERAPY OF NEONATAL JAUNDICE

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NEONATAL JAUNDICE

Bilirubin is a tetrapyrrole that exists in normal human blood at levels of 0,8mg/100ml (GRAY, 1963). This level reflects the equilibrium between the production of bilirubin in hemoglobin degradation and the elimination of bilirubin by the liver. Bilirubin is practically water insoluble and readily enters lipid membranes. In its free form it can not pass through either the canalicular membrane of the hepatocyte or the renal system. Bilirubin is eliminated from the body by processing in the liver where it is converted to bilirubin glucuronate by bilirubin glucuronyl transferase.

Jaundice, also called icterus, results from having excessive blood bilirubin. Regurgitation jaundice occurs when conjugated bilirubin leaks back into the blood system. This is caused by blockage of the biliary duct. Retention jaundice occurs when free bilirubin can not exit from the blood. This is caused by liver disfunction or by lack of conjugating enzyme. In retention jaundice serum bilirubin approaches concentrations of 20mg/100ml and begins to enter the basal nuclei of the brain (GRAY, 1963). This condition, kernicterus, leads to brain damage and is a common cause of cerebral palsy.

All newborn infants pass through a transition period in which serum bilirubin increases. Since fetal bilirubin is disposed of through the placental membrane, the conjugating enzyme is not activated until after birth. The condition becomes dangerous when the transition period is long, as in premature birth. If during this period there is excessive hemolysis, serum bilirubin can reach dangerous levels. These cases, separate or together, lead to neonatal jaundice. Until phototherapy was developed, treatment was by massive blood transfusion. Now this expensive and risky procedure is only used where phototherapy can not reduce serum bilirubin rapidly enough to avoid kernicterus.

PHOTOTHERAPY

Phototherapy is the treatment of disease by light, either visible or ultraviolet. It is

neither new nor uncommon. Tuberculosis and vitamin D deficiency have long been treated by this method. Numerous experimental procedures have had partial success in treating superficial viral infection by dye treatment in conjunction with phototherapy (LYTLE, 1977). Vitiligo can be cosmetically treated by inducing skin pigmentation with psoralen and ultraviolet light.

Blue light has the remarkable capacity to substantially reduce the level of serum bilirubin in newborn infants. This light treatment is a standard form of phototherapy and is universally used to treat neonatal jaundice. By 1958 it was shown that this is a relatively sure method (kernicterus is prevented), and that it appears to cause no immediate deleterious side reactions (CREMER *et al.*, 1958). Soon after that date the precaution was added to blindfold the infant's eyes to safeguard the retina, which is especially sensitive to high-intensity light during this formative period.

Clearly phototherapy is an effective way to treat neonatal jaundice. However, fear of damaging photochemical reactions have periodically been expressed (ODELL *et al.*, 1976), and the anemia sometimes associated with phototherapy has been attributed to light sensitized oxidations of components of red blood cells. Long range studies of patients receiving this temporary treatment have yet to statistically differentiate normal and treated patients in the years following treatment (LUCEY *et al.*, 1973).

BILIRUBIN PHOTOCHEMISTRY

The literature on bilirubin photochemistry has continually grown both because of its complexity and because *in vitro* chemical studies did not fully explain why phototherapy is effective. A comprehensive review of this subject has been recently published (LIGHTNER, 1977). The establishment of the X-ray crystal structure of bilirubin (BONNETT *et al.*, 1976) gave an exciting thrust to experimental work by suggesting an explanation for the enigmatic solubility behavior of this tetrapyrrole. In its normal form bilirubin IX-alpha is completely hydrogen bonded to itself with six hydrogen bonds. This prevents the system from hydrogen bonding to a solvent, such as water, or interacting by polar forces (since the polar groups are held in interior positions). Only by breaking these bonds can bilirubin be forced into aqueous solution. This can be effected in neutral solution (like blood) by blue light, which causes the large molecule to undergo a geometrical configuration change. In this new configuration the polar groups are exposed to the solvent.

The current explanation of phototherapy is based on this idea. That is the light treatment of retention jaundice changes the solubility properties so the intact bilirubin can be passed through the liver (McDONAGH, 1977). Excessive serum bilirubin accumulates in the skin, and it is here that the main photochemical changes occur. Bilirubin absorbs light and is converted to a metastable isomer, which does not have to be conjugated to be eliminated by the liver. After entering the intestine the bilirubin reverts to its

previous stable form, making it appear as if it had passed through the liver in this form. This mechanism is unproved, but no other proposal exists that can explain how unconjugated bilirubin passes into the intestine in direct response to light.

Secondary in explaining phototherapy are the degradation photooxidations, which were intensely studied and originally thought to be the primary mechanism of eliminating serum bilirubin in phototherapy. (FOOTE and CHING, 1975). Bilirubin reacts extraordinarily fast with singlet molecular oxygen to form water-soluble dipyrroles and monopyrroles. In the presence of light and oxygen bilirubin sensitizes the production of singlet oxygen, which can attack various fats, proteins, and amino acids. Although there may be some destructive processes in phototherapy because of this side reaction, the damage is marginal since the bilirubin also removes the excited oxygen by quenching or reacting with it at the moment of its production.

CLINICAL PRACTISE

Standard practise for jaundice prone neonates is to closely monitor total serum bilirubin. This is now known to give inadequate information to properly treat neonatal jaundice. The level of serum albumin must be considered as this protein binds tightly to bilirubin, and thus prevents it from causing damage. Only when the level of serum bilirubin exceeds the capacity of the serum albumin to bind it does the problem begin.

A fluorescence technique that measures the reserve binding capacity of the blood is being developed. It utilizes differences in the fluorescence quantum yields of bilirubin, bilirubin bound to albumin, and bilirubin solubilized in detergent micelles. This method is rapid and only moderately complex, but it requires a sensitive spectrofluorimeter. Five fluorescent assays are made: 1) a drop of blood; 2) a drop of blood with detergent added; 3) a drop of blood with bilirubin added; 4) a blank; and 5) a standard. From these 5 values (using only 3 drops of blood) and standard curves the reserve binding capacity of the blood can be accurately determined. This technique will soon be available and will add new safeguards to newborn infant care (LAMOLA, 1977).

RESUMO

Este artigo apresenta novos aspectos do tratamento e conhecimento da icterícia do recém-nascido. Uma explicação do mecanismo da fototerapia é baseada em mudanças da solubilidade da bilirubina produzida pela ação da luz azul. Uma nova técnica de fluorescência foi desenvolvida para medir a capacidade da albumina para se ligar à bilirubina. A fototerapia parece ser ainda o melhor tratamento para a icterícia do recém-nascido.

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