~~A.~~ **METHODS FOR TREATING HYPERBILIRUBINEMIA WITH STANNSOPORFIN**

~~B. CROSS REFERENCE~~

~~[0001] This application claims the benefit of U.S. Provisional Application Serial No. 61/565,842 entitled "Methods For Treating Hyperbilirubinemia With Stannsoporfin" filed December 1, 2011 which is incorporated herein by reference in its entirety.~~

~~C.~~ BACKGROUND

[~~0002~~0001] Raised bilirubin levels may lead to potentially dangerous conditions, particularly in infants. In some cases, elevated bilirubin levels result from conditions that cause an increase in bilirubin production and in others with conditions affecting removal of bilirubin. In some instances, it is a combination. Increased bilirubin levels may lead to hyperbilirubinemia which can be dangerous to a patient. Accordingly, more and different treatments for reducing bilirubin production, increasing bilirubin excretion, or both, are desirable as are other methods of treating hyperbilirubinemia or increased bilirubin production.

~~D.~~ SUMMARY

[~~0002a~~0002] In one aspect, there is provided a use of a therapeutic amount of stannsoporfin for the manufacture of a medicament for treating hyperbilirubinemia or the symptoms thereof in an infant, wherein no exclusion factor is present and at least one of a baseline total bilirubin level is elevated above a predetermined threshold and at least one risk factor is present in said infant with hyperbilrubinemia; wherein the predetermined threshold is below the threshold for administration of phototherapy according to AAP guidelines; wherein said medicament is to be administered to said infant; and wherein the infant is Coombs positive.

[0003] The present disclosure further relates to methods of treating hyperbilirubinemia with a metalloporphyrin. More particularly, embodiments disclosed include methods of treating hyperbilirubinemia or the symptoms thereof in an infant.

[0051] Some embodiments are directed to methods for treating rising bilirubin levels comprising: establishing a baseline bilirubin level in a patient at risk for hyperbilirubinemia at a predetermined age; administering to the patient a therapeutic amount of stannsoporfin after the baseline is established. In some embodiments, the predetermined age is about 6 hours, about 12 hours, or about 24 hours from birth. In some embodiments, a baseline reading at the AAP nomogram threshold for administering phototherapy or up to 3.0mg/dL below the AAP nomogram threshold for administering phototherapy indicates treatment is required.

[0052] Some embodiments are directed to methods of treating hyperbilirubinemia comprising: administering a therapeutic amount of stannsoporfin to a patient in need thereof to achieve a Cmax of at least 5000ng/mL. In some embodiments, the therapeutic amount of stannsoporfin is 1.5mg/kg and achieves a Cmax of about 6450 ng/mL. In some embodiments, the therapeutic amount of stannsoporfin is 3.0 mg/kg and achieves a Cmax of about 11500 ng/mL. In some embodiments, the therapeutic amount of stannsoporfin is 4.5 mg/kg and achieves a Cmax of about 20400 ng/mL. In some embodiments, Cmax is achieved at a Tmax of about 1.5 hours to about 2.5 hours.

[0053] Since embodiments herein are directed at treating hyperbilirubinemia with the idea of minimizing the need for phototherapy, the incidence of or need for exchange transfusion or central nervous system injury may also be reduced.

~~E.~~ BRIEF DESCRIPTION OF THE FIGURES

[0054] Figure 1 is the AAP Nomogram for initiating phototherapy based on age of infant and total serum bilirubin.

[0055] Figure 2 is the AAP Nomogram for initiating exchange therapy based on age of infant and total serum bilirubin.

[0056] Figure 3 is a nomogram for administering a metalloporphyrin based on a shift in bilirubin level.

[0057] Figure 4 is a nomogram for administering a metalloporphyrin based on a shift in age.

[0069] Figure 14 depicts percent Change from Baseline in Unadjusted TSB±SE (ITT Population N=58).

[0070]

~~F.~~ DETAILED DESCRIPTION

[0071] Infant hyperbilirubinemia (also known as infant jaundice or neonatal hyperbilirubinemia) occurs in a newborn when the liver is unable to conjugate bilirubin so it can be excreted at a rate commensurate with bilirubin formation. Bilirubin comes from the catabolism of heme as part of the physiological conversion from fetal to adult hemoglobin at birth, or as part of a pathological hemolytic process. The enzyme heme oxygenase oxidizes heme to biliverdin; the enzyme biliverdin reductase then reduces the biliverdin to bilirubin. Bilirubin at high serum levels is a neurotoxic substance. In adult humans, the liver rapidly converts bilirubin into a conjugated, excretable form. In newborn humans, however, the liver is still developing, and uptake and conjugation by the liver is not as efficient as in adults. Additionally, hemolysis may be taking place at a greater relative rate than in adults. All of these factors can lead to excessive bilirubin in the infant. For some infants, high serum levels of bilirubin can have detrimental physiological consequences. Bilirubin is yellow, and infants with excess bilirubin appear jaundiced, having a yellow tinge to their skin and to the whites of their eyes.

[0072] Infants who have highly elevated serum levels of bilirubin are at risk of developing kernicterus, a rare but potentially devastating neurological disorder which can result in severe life-long disabilities including cerebral palsy, athetosis, hearing loss, and vision problems. Because early hospital discharge can impair the detection of hyperbilirubinemia in infants, effective means of treating hyperbilirubinemia rapidly are desirable. The unique medical status of a newborn also requires that any means of treatment be as safe as possible, as side effects that are tolerable in adults may be completely unacceptable in neonates.

[0073] Currently approved and commonly used treatments for hyperbilirubinemia include phototherapy and exchange transfusion. Phototherapy involves irradiating the newborn with light in the 430 to 490 nm range (blue light). The light converts bilirubin into lumirubin and photobilirubin, which are less toxic water-soluble photoisomers that are more readily excreted by the infant, and thus can result in a reduction of bilirubin levels. The

[00248] In some embodiments, the therapeutic amount of the metalloporphyrin is from about 0.75 mg/kg to about 5 mg/kg. In some embodiments, the therapeutic amount of the metalloporphyrin is selected from 0.75 mg/kg, 1.5 mg/kg, 3.0 mg/kg and 4.5 mg/kg. In some embodiments, the therapeutic amount of the stannsoporfin is from about 0.75 mg/kg to about 5 mg/kg. In some embodiments, the therapeutic amount of the stannsoporfin is selected from 0.75 mg/kg, 1.5 mg/kg, 3.0 mg/kg and 4.5 mg/kg.

[00249] Some embodiments are directed to the use of a metalloporphyrin in the manufacture of a medicament for the treatment of rising bilirubin levels comprising: establishing a baseline bilirubin level in a patient at risk for hyperbilirubinemia at a predetermined age; administering to the patient a therapeutic amount of stannsoporfin after the baseline is established. In some embodiments, the predetermined age is about 6 hours, about 12 hours, or about 24 hours from birth. In some embodiments, a baseline reading at the AAP nomogram threshold for administering phototherapy or up to 3.0mg/dL below the AAP nomogram threshold for administering phototherapy indicates treatment is required.

[00250] Some embodiments are directed to the use of a metalloporphyrin in the manufacture of a medicament for the treatment hyperbilirubinemia comprising: administering a therapeutic amount of stannsoporfin to a patient in need thereof to achieve a Cmax of at least 5000ng/mL. In some embodiments, the therapeutic amount of stannsoporfin is 1.5mg/kg and achieves a Cmax of about 6450 ng/mL. In some embodiments, the therapeutic amount of stannsoporfin is 3.0 mg/kg and achieves a Cmax of about 11500 ng/mL. In some embodiments, the therapeutic amount of stannsoporfin is 4.5 mg/kg and achieves a Cmax of about 20400 ng/mL. In some embodiments, Cmax is achieved at a Tmax of about 1.5 hours to about 2.5 hours.

[00251] This invention and embodiments illustrating the method and materials used may be further understood by reference to the following non-limiting examples.

~~G.~~ EXAMPLES

[00252] Phase 2b, Multicenter, Single-dose, Blinded, Randomized, Placebo-controlled, Dose-escalation, Safety and Efficacy Trial of Stannsoporfin in Neonates with Hyperbilirubinemia