METHODS FOR TREATING HYPERBILIRUBINEMIA WITH STANNSOPORFIN

BACKGROUND

[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.

SUMMARY

[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 2004 AAP guidelines; wherein said medicament is to be administered to said infant; ~~and~~ wherein the infant is Coombs positive;

wherein the at least one risk factor is selected from hemolytic disease, ABO blood type incompatibility, anti-C Rh incompatibility, anti-c Rh incompatibility, anti-D Rh incompatibility, anti-E Rh incompatibility, anti-e Rh incompatibility, G6PD deficiency and combinations thereof; and

wherein the at least one exclusion factor is selected from a clinical suggestion of neonatal thyroid disease, current uncontrolled thyroid disease in the mother excluding maternal Hashimoto's, treatment or need for treatment in the infant with medications that may prolong the QT interval excluding eythromycin ointment for eye prophylaxis, a family history of Long QT syndrome, a family history of sudden infant death syndrome, known porphyrias, risk factors for porphyrias, a family history of porphyrias, a maternal history of systemic

lupus erythematosus, maternal use of phenobarbital 30 days before, or after delivery, if breastfeeding, maternal current drug or alcohol abuse, maternal history of drug or alcohol abuse, an Apgar score less than or equal to 6 at age 5 minutes, congenital anomalies or infections, acidosis, sepsis, hepatitis; a risk of requiring surgery or exposure to operating room lights in the future, cardiorespiratory distress defined as a respiratory rate >60 breaths per minute, a diagnosis of transient tachypnea of the newborn, abnormal auditory or ophthalmologic findings, clinically significant abnormalities on a screening laboratory evaluation, elevated direct or conjugated bilirubin (>1.0 mg/dL if the TSB is <5.0 mg/dL or >20% of the TSB if the TSB is ≥5.0 mg/dL), persistent hypoglycemia (blood glucose <40 mg/dL) despite standard-of-care treatment, liver diseases defined as ALT and/or AST greater than 2 times the upper limit of normal [ULN], abnormal renal function defined as creatinine and/or blood urea nitrogen greater than 2 times the ULN, any blood smear finding of structural red cell abnormalities, such as spherocytosis, not caused by isoimmune hemolysis, temperature instability defined as temperature consistently (3 consecutive times) greater than 36°C and/or greater than 37.5°C axillary, use of photosensitizing drugs or agents; dehydration, defined by hypernatremia, serum sodium greater than ULN, use of intravenous immunoglobulin (IVIG) or albumins, post-delivery treatment with medications that are known or suspected to displace bilirubin from albumin (e.g., ceftriaxone or sulfa-based antibiotics), morbid conditions including but not limited to pulmonary disease, cardiovascular disease), exposure to any investigational medications or devices after delivery, participation in a clinical trial and combinations thereof.

[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.

[0004] Some embodiments are directed to methods of treating hyperbilirubinemia or the symptoms thereof in an infant, the method comprising: administering a therapeutic amount of a metalloporphyrin to the infant with hyperbilirubinemia where 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; wherein the hyperbilirubinemia or symptoms thereof is treated.

[0005] Some embodiments further comprise determining baseline total bilirubin levels in the infant. In some embodiments, baseline total bilirubin levels comprises total serum bilirubin levels, total cutaneous bilirubin or a combination thereof.

CLAIMS

What is claimed:

1. 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 2004 AAP guidelines;

wherein said medicament is to be administered to said infant; ~~and~~

wherein the infant is Coombs positive;

wherein the at least one risk factor is selected from hemolytic disease, ABO blood type incompatibility, anti-C Rh incompatibility, anti-c Rh incompatibility, anti-D Rh incompatibility, anti-E Rh incompatibility, anti-e Rh incompatibility, G6PD deficiency and combinations thereof; and

wherein the at least one exclusion factor is selected from a clinical suggestion of neonatal thyroid disease, current uncontrolled thyroid disease in the mother excluding maternal Hashimoto's, treatment or need for treatment in the infant with medications that may prolong the QT interval excluding evthromycin ointment for eye prophylaxis, a family history of Long QT syndrome, a family history of sudden infant death syndrome, known porphyrias, risk factors for porphyrias, a family history of porphyrias, a maternal history of systemic lupus erythematosus, maternal use of phenobarbital 30 days before, or after delivery, if breastfeeding, maternal current drug or alcohol abuse, maternal history of drug or alcohol abuse, an Apgar score less than or equal to 6 at age 5 minutes, congenital anomalies or infections, acidosis, sepsis, hepatitis; a risk of requiring surgery or exposure to operating room lights in the future, cardiorespiratory distress defined as a respiratory

rate >60 breaths per minute, a diagnosis of transient tachypnea of the newborn, abnormal auditory or ophthalmologic findings, clinically significant abnormalities on a screening laboratory evaluation, elevated direct or conjugated bilirubin (>1.0 mg/dL if the TSB is <5.0 mg/dL or >20% of the TSB if the TSB is ≥5.0 mg/dL), persistent hypoglycemia (blood glucose <40 mg/dL) despite standard-of-care treatment, liver diseases defined as ALT and/or AST greater than 2 times the upper limit of normal [ULN], abnormal renal function defined as creatinine and/or blood urea nitrogen greater than 2 times the ULN, any blood smear finding of structural red cell abnormalities, such as spherocytosis, not caused by isoimmune hemolysis, temperature instability defined as temperature consistently (3 consecutive times) greater than 36°C and/or greater than 37.5°C axillary, use of photosensitizing drugs or agents; dehydration, defined by hypernatremia, serum sodium greater than ULN, use of intravenous immunoglobulin (IVIG) or albumins, post-delivery treatment with medications that are known or suspected to displace bilirubin from albumin (e.g., ceftriaxone or sulfa-based antibiotics), morbid conditions including but not limited to pulmonary disease, cardiovascular disease), exposure to any investigational medications or devices after delivery, participation in a clinical trial and combinations thereof.

2. The use of claim 1, wherein total bilirubin levels is to be determined following administration of the medicament from ~~about~~ 6 and to ~~about~~ 72 hours after administering the medicament to the infant to determine if phototherapy should be initiated based upon the 2004 AAP guidelines.

3. The use of claim 1, wherein the medicament is to be administered within 36 hours of birth of the infant.

~~4. The use of claim 1, wherein the at least one risk factor is selected from hemolytic disease, ABO blood type incompatibility, anti-C Rh incompatibility, anti-c Rh incompatibility, anti-D Rh incompatibility, anti-E Rh incompatibility, anti-e Rh incompatibility, G6PD deficiency and combinations thereof.~~

~~54~~. The use of claim 1, wherein the at least one risk factor is selected from hemolytic disease, anti-C Rh incompatibility, anti-c Rh incompatibility, anti-D Rh incompatibility, anti-E Rh incompatibility, anti-e Rh incompatibility, and G6PD deficiency and combinations thereof.

~~6. The use of claim 1, wherein the at least one exclusion factor is selected from a clinical suggestion of neonatal thyroid disease, current uncontrolled thyroid disease in the mother excluding maternal Hashimoto's, treatment or need for treatment in the infant with medications that may prolong the QT interval excluding eythromycin ointment for eye prophylaxis, a family history of Long QT syndrome, a family history of sudden infant death syndrome, known porphyrias, risk factors for porphyrias, a family history of porphyrias, a maternal history of systemic lupus erythematosus, maternal use of phenobarbital 30 days before, or after delivery, if breastfeeding, maternal current drug or alcohol abuse, maternal history of drug or alcohol abuse, an Apgar score less than or equal to 6 at age 5 minutes, congenital anomalies or infections, acidosis, sepsis, hepatitis; an excess risk of requiring surgery or exposure to operating room lights in the foreseeable future, cardiorespiratory distress defined as a respiratory rate >60 breaths per minute, a diagnosis of transient tachypnea of the newborn, abnormal auditory or ophthalmologic findings, clinically significant abnormalities on a screening laboratory evaluation, elevated direct or conjugated bilirubin (>1.0 mg/dL if the TSB is <5.0 mg/dL or >20% of the TSB if the TSB is ≥5.0 mg/dL), persistent hypoglycemia (blood glucose <40 mg/dL) despite standard of care treatment, liver diseases defined as ALT and/or AST greater than 2 times the upper limit of normal [ULN], abnormal renal function defined as creatinine and/or blood urea nitrogen greater than 2 times the ULN, any blood smear finding of~~

~~structural red cell abnormalities, such as spherocytosis, not caused by isoimmune hemolysis, temperature instability defined as temperature consistently (3 consecutive times) greater than 36°C and/or greater than 37.5°C axillary, use of photosensitizing drugs or agents; dehydration, defined by hypernatremia, serum sodium greater than ULN, use of intravenous immunoglobulin (IVIG) or albumins, post-delivery treatment with medications that are known or suspected to displace bilirubin from albumin (e.g., ceftriaxone or sulfa-based antibiotics), serious morbid conditions including but not limited to pulmonary disease, cardiovascular disease), exposure to any investigational medications or devices after delivery, participation in a clinical trial and combinations thereof.~~

~~75~~. The use of claim 1, wherein the predetermined threshold is selected from ~~about~~ 1-3 mg/dL below a threshold for administration of phototherapy to an infant up to ~~about~~ 12 hours of age per the 2004 AAP guidelines, ~~about~~ 1 mg/dL below a threshold for administration of phototherapy to an infant up to ~~about~~ 12 hours of age per the 2004 AAP guidelines, ~~about~~ 2 mg/dL below a threshold for administration of phototherapy to an infant up to ~~about~~ 12 hours of age per the 2004 AAP guidelines, at the threshold for administration of phototherapy to an infant up to ~~about~~ 12 hours of age per the 2004 AAP guidelines, ~~about~~ 1-3mg/dL below a threshold for administration of phototherapy to an infant from ~~about~~ 12 to 48 hours of age per the 2004 AAP guidelines, is ~~about~~ 2 mg/dL below a threshold for administration of phototherapy to an infant from ~~about~~ 12 to 48 hours of age per the 2004 AAP guidelines, ~~about~~ 3 mg/dL below a threshold for administration of phototherapy to an infant from ~~about~~ 12 to 48 hours of age per the 2004 AAP guidelines, and ~~about~~ 1 to ~~about~~ 3 mg/dL below the threshold for administration of phototherapy according to 2004 AAP nomogram corresponding to the infants age.

~~86~~. The use of claim 1, wherein the medicament is to be administered at a time selected from within ~~about~~ 6 hours of birth,

within ~~about~~ 12 hours of birth, within ~~about~~ 24 hours of birth and within ~~about~~ 48 hours of birth.

~~9~~7. The use of claim 1, wherein the infant is of a gestational age from ~~about~~ 35 to ~~about~~ 43 weeks.

~~10~~8. The use of claim 1, wherein the therapeutic amount of the stannsoporfin is from ~~about~~ 0.75 mg/kg to ~~about~~ 5 mg/kg of the infant's weight.

~~11~~9. The use of claim 1, wherein 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 of the infant's weight.

~~12~~10. The use of claim 1, wherein the medicament is to be administered by intramuscular injection.

~~13~~11. The use of claim 1, wherein phototherapy is to be administered where total bilirubin levels following administration of the medicament are above the baseline total bilirubin levels.

~~14~~12. The use of claim 1, wherein total bilirubin levels are at least 5% below the baseline total bilirubin levels 24 hours after administration of the medicament to the infant, wherein total bilirubin levels are at least 10% below the baseline total bilirubin levels 48 hours after administration of the medicamentto the infant,or wherein post treatment total bilirubin levels are at least 20% below the baseline total bilirubin levels 72 hours after administration of the medicament to the infant.