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] 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] 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~~wherein the hyperbilirubinemia or symptoms thereof is treated~~.

[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.

[00174] In some embodiments, the metalloporphyrin may be tin (IV) mesoporphyrin IX dichloride. As used herein, tin (IV) mesoporphyrin IX dichloride includes tin 4+ mesoporphyrin IX dichloride and stannsoporfin (SnMP). Tin (IV) mesoporphyrin IX dichloride can be obtained according to a variety of methods, for example, through the methods disclosed in U.S. Pat. No. 6,818,763, U.S. Pat. No. 7,375,216, or co-pending U.S. Application No. 11/867,559 filed on Oct. 4, 2007~~, which are incorporated herein by reference~~. However, it should be understood that other methods can be used to produce mesoporphyrin halides such as tin mesoporphyrin IX dichloride, and the present invention is not limited to a particular method of mesoporphyrin production.

[00175] In certain embodiments, the metalloporphyrin may be present in a substantially pure form in the pharmaceutical preparation. In some embodiments, the overall purity of the metalloporphyrin in the pharmaceutical preparation may be at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 98.5%, at least about 99%, or at least about 99.5%. In an embodiment, each individual product-related impurity in the pharmaceutical preparation may be in an amount of less than about 1%, less than about 0.5%, less than about 0.3%, or less than about 0.1% of the preparation. In an embodiment, any individual product-related impurity present is present in an amount of less than about 0.5%, less than about 0.3%, less than about 0.2%, less than about 0.15%, less than about 0.1%, less than about 0.09%, less than about 0.08%, or less than about 0.07% of the preparation.

[00176] The pharmaceutical preparation may be in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged in vials or ampules.

[00177] The quantity of active component in a unit dose preparation may be varied or adjusted from about 0.1 to about 50 mg, preferably 0.1 to about 40 mg, and more preferably 0.1 to about 20 mg according to the particular application and the potency of the active component and size of the patient. The composition can, if desired, also contain other compatible therapeutic agents.

[00178] In therapeutic use as agents for treating hyperbilirubinemia, the compounds utilized in the pharmaceutical methods of this invention are administered at the initial dosage of about 0.1 mg to about 20 mg per kilogram body weight (IM). In certain embodiments, treatment with the metalloporphyrin is a one-time single dose treatment. In some embodiments, the metalloporphyrin is administered in a dosage of from about 0.5 mg to

readmitted to the hospital for PT after discharge, and this did not occur in stannsoporfin-treated subjects.

[00366] Analysis of exposure data showed that stannsoporfin was rapidly and well absorbed from an IM injection, and the absorption of stannsoporfin followed first-order linear kinetics, with peak plasma concentrations observed within 1 hour post-treatment. The elimination half-life was approximately 10 hours.

[00367] Overall, exposure to stannsoporfin was well tolerated, with no statistically significant differences between the 3 stannsoporfin treatment groups and the placebo group in the incidence of TEAEs. All TEAEs except one (a contusion) were considered mild or moderate in severity. There were 4 SAEs reported, an anemia, a meningitis, and 2 subjects with hyperbilirubinemia, all of which were considered not related to the study drug and were either mild or moderate in severity.

[00368] In the clinical laboratory evaluation, the majority of hematological and clinical chemistry parameters showed no dose-related trends or marked differences in mean values between the stannsoporfin-treated groups and the placebo group, all mean values for all parameters and treatment groups were well within normal ranges, and most returned to baseline levels at Day 14. For clinical laboratory changes reported as AEs during the study, only a hemoglobin increased and a thrombocytopenia were considered possibly related to the study drug.

[00369] There were no concerning dose-related trends or marked differences between treatment groups observed in vital signs, physical examinations, dermatological evaluations, audiology examinations, ophthalmological evaluations, or neurological evaluations. In the ECG evaluations, there were no marked dose-related trends in either changes from baseline or absolute values.

[00370] In conclusion, this multicenter, randomized, blinded study in 58 neonates with hyperbilirubinemia demonstrated similar safety across 3 dose levels up to 4.5 mg/kg, with predictable linear PK for stannsoporfin, and efficacy as a dose-related reduction in adjusted and unadjusted TSB levels from 12 hours onward after a single dose.

[00371] ~~It is to be understood that the embodiments disclosed herein are not limited to the particular processes, compositions, or methodologies described, as these may vary.~~ It is ~~also~~ to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only~~, and is not intended to limit the scope of the present invention~~. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present invention, the preferred methods, devices, and materials are now described. ~~All publications mentioned herein are incorporated by reference in their entirety.~~ Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[00372] Optical Isomers--Diastereomers--Geometric Isomers—Tautomers. Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereomers. The present invention includes all such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers. The formulas are shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of such formulas and pharmaceutically acceptable salts thereof. Diastereoisomeric pairs of enantiomers may be separated by, for example, fractional crystallization from a suitable solvent, and the pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent or on a chiral HPLC column. Further, any enantiomer or diastereomer of a compound of the general formula may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

~~[00373] It must also be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" is a reference to one or more compounds and equivalents thereof known to those skilled in the art, and so forth.~~

[00373~~4~~] As used herein, the term "about" means plus or minus 10% of the numerical value of the number with which it is being used. Therefore, about 50% means in the range of 45%-55%.

[00374~~5~~] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic directly into or onto a target tissue or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term "administering", when used in conjunction with a metalloporphyrin, can include, but is not limited to, providing the metalloporphyrin into or onto the target tissue; providing the metalloporphyrin systemically to a patient by, e.g., intravenous injection whereby the therapeutic reaches the target tissue. "Administering" a composition may be

accomplished by injection, topical administration, or by either method in combination with other known techniques.

[003756] The term "animal," "subject" or "patient" as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. Most preferably, "animal," "subject," or "patient" refers to humans, particularly infants.

[003767] The term "improves" is used to convey that the present invention changes either the appearance, form, characteristics and/or the physical attributes of the tissue to which it is being provided, applied or administered. The change in form may be demonstrated by any of the following alone or in combination: enhanced appearance of the skin; reduced need for exchange transfusion, reduced need for phototherapy, decrease in bilirubin levels, decrease in jaundice, prevention or reduction of zone 5 jaundice, and/or reduction in the length of hospital stay.

[003778] The term "inhibiting" includes the administration of a compound of the present invention to prevent the onset of the symptoms, alleviating the symptoms, or eliminating the disease, condition or disorder.

[003789] By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[003798] As used herein, the phrase "physiological osmolarity" means the drug product or composition, when administered to a patient does not cause irritation or an adverse reaction. A suitable range for the osmolarity according to certain embodiments may be from about 270 to about 328 mOsmol/L, and more preferably from about 280 to about 300 mOsmol/L osmolarity.

[003801] As used herein, the term "therapeutic" means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In part, embodiments of the present invention are directed to the treatment of hyperbilirubinemia or the reduction in total serum bilirubin.

[003812] A "therapeutic amount" or "effective amount" of a composition is a predetermined amount calculated to achieve the desired effect, i.e., to treat, prevent or reduce jaundice or hyperbilirubinemia, to reduce bilirubin production, to increase bilirubin excretion, or combination thereof, or to reduce total serum bilirubin and/or total cutaneous bilirubin, or to otherwise delay, inhibit, or slow the progression of hyperbilirubinemia. The activity contemplated by the present methods includes both medical therapeutic and/or prophylactic treatment, as appropriate. The specific dose of a compound administered according to this

invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration, and the condition being treated. The compounds are effective over a wide dosage range. However, it will be understood that the effective amount administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, and the chosen route of administration~~, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way~~. A therapeutic amount of compound of this invention is typically an amount such that when it is administered in a physiologically tolerable excipient composition, it is sufficient to achieve an effective systemic concentration or local concentration in the tissue.

[003823] The terms "treat," "treated," or "treating" as used herein refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

[003834] As used herein, the term "baseline" is refers to an infant's serum bilirubin levels prior to administration of therapeutic treatment and prophylactic or preventative measures. In some embodiments, an infant's baseline serum bilirubin levels serves to measure changes in the an infant's serum bilirubin levels.

[003845] Although the present invention has been described in considerable detail with reference to certain preferred embodiments thereof, other versions are possible. ~~Therefore, the spirit and scope of the appended claims should not be limited to the description and the preferred versions contained within this specification.~~

~~H.~~ 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 AAP guidelines;

wherein said medicament is to be administered to said infant; and wherein the infant is Coombs positive.

~~2. The use of claim 1, wherein the infant is Coombs positive.~~

~~32~~. 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 AAP guidelines.

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

~~54~~. 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.

~~65~~. 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.

~~76~~. 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.

~~8~~7. 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 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 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 AAP guidelines, at the threshold for administration of phototherapy to an infant up to about 12 hours of age per the 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 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 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 AAP guidelines, and about 1 to about 3 mg/dL below the threshold for administration of phototherapy according to AAP nomogram corresponding to the infants age.

~~9~~8. 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.

~~10~~9. The ~~method~~ use of claim 1, wherein the infant is of a gestational age from about 35 to about 43 weeks.

~~11~~10. 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.

~~12~~11. 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.

~~13~~12. The use of claim 1, wherein the medicament is to be administered by intramuscular injection.

~~14~~13. 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.

1415. 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.