

Exploring the Therapeutic Potential and Challenges of Tin Mesoporphyrin (SnMP) in the Treatment of Neonatal Hyperbilirubinemia

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Abstract. Hyperbilirubinemia is a common neonatal condition that manifests itself as elevated levels of bilirubin in the blood and, if left untreated, may lead to severe neurological damage. Existing treatments, such as phototherapy and blood exchange therapy, are usually administered after bilirubin has already reached dangerous levels. Tin mesoporphyrin (SnMP), a potent heme oxygenase (H.O.) inhibitor, presents a preventive approach, potentially reducing bilirubin production before it reaches critical levels. This review evaluates SnMP's synthesis, mechanism of action, and metabolic pathway, emphasizing its effectiveness compared to other H.O. inhibitors such as Zinc protoporphyrin (ZnPP). Contrary to widespread fears, we present clinical findings showing that SnMP phototoxicity does not pose a significant risk in clinical Settings, supporting SnMP as a safer and more effective alternative to current therapies. Our analysis shows that with further research and optimization of its formulation, SnMP can be a breakthrough therapy for effectively and safely preventing severe hyperbilirubinemia.

Keywords: hyperbilirubinemia, Tin mesoporphyrin (SnMP), stannoporphin, heme oxygenase inhibitors, metalloporphyrin, phototherapy, neonatal jaundice, bilirubin, Zinc protoporphyrin (ZnPP), synthesis, metabolism

1. Introduction

In 2024, the primary method to reduce the hemolytic rate in newborns with severe hemolytic jaundice is performing a double-volume exchange transfusion, which involves replacing hemolyzing red blood cells with donor adult red blood cells. Metalloporphyrins, which inhibit heme oxygenase—the enzyme responsible for controlling bilirubin production from heme—are being investigated as potential treatments for hyperbilirubinemia. Among these, Tin mesoporphyrin (SnMP) has shown positive results in both animal and human trials, while Zinc protoporphyrin (ZnPP) has only been tested in animals. However, neither drug has received approval for clinical use in the United States [1]. This study discovered the properties of SnMP that show the potentiality to treat hyperbilirubinemia as a replacement for exchange transfusion and phototherapy.

2. Method

This review conducted a comprehensive literature search, primarily using databases such as PubMed, Google Scholar, and Web of Science. Search keywords include “tin protoporphyrin (SnMP),” “heme oxygenase inhibitors,” “hyperbilirubinemia treatment” and so on. The literature search focuses on

peer-reviewed articles, clinical trials, and related patents. Articles involving human studies were selected, as well as detailed information on the synthesis, efficacy, or side effects of SnMP. Articles that have yet to be peer-reviewed are excluded. After the literature is selected, the full text is reviewed, the critical information is extracted, and the extracted data is analyzed and summarized. A synthesis was carried out by comparing the results of different studies.

3. Result

3.1. Introduction of Hyperbilirubinemia and Bilirubin

Hyperbilirubinemia is a condition where bilirubin, a waste product from the breakdown of old red blood cells usually expelled through the intestines, accumulates in the blood. This buildup leads to a yellowish tint in the eyes and skin, commonly known as jaundice. While low bilirubin levels are generally not harmful, elevated levels can spread to brain tissues, potentially causing seizures and brain damage. Factors like premature birth, infections, or certain blood disorders can accelerate the accumulation of bilirubin to harmful levels [2,3].

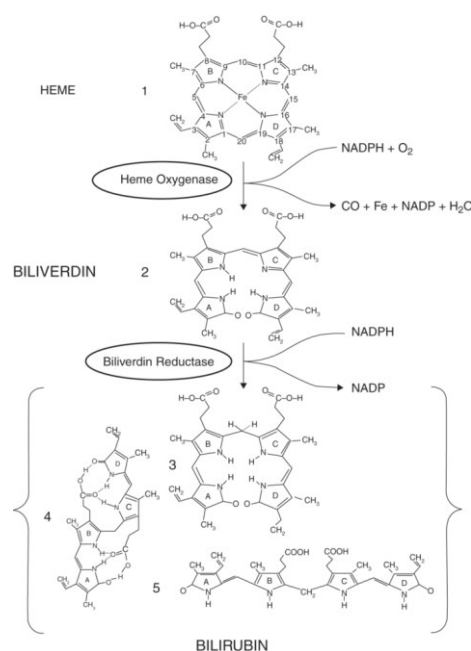


Figure 1. The Formation of Bilirubin. Adapted from Satrom and Gourley.

The formation of bilirubin begins with the fragmentation of the tetrapyrrole ring in protoheme (protoporphyrin IX), resulting in the creation of a linear tetrapyrrole known as biliverdin, as shown in Fig. 1. This process occurs when heme, also referred to as iron protoporphyrin (FePP), binds to the enzyme microsomal heme oxygenase (H.O.), which is an enzyme with antioxidant, cytoprotective, and immunoregulatory properties that facilitates the breakdown of heme [4]. Heme oxygenase “is located within the endoplasmic reticulum,” within the cytoplasm of eukaryotic cells, where it catabolizes heme [5]. The reaction requires the presence of cytochrome P-450 reductase, reduced nicotinamide-adenine dinucleotide phosphate (NADPH), and oxygen. NADPH is a coenzyme, a biological molecule that enhances the catalytic function of an enzyme, and it serves as a cofactor acting as an electron donor in many organisms, including enzymes [6].

The enzyme facilitates its oxidative ring cleavage, converting the iron within the porphyrin from FeIII to FeII and adding a hydroxyl group to the α -methine carbon. This carbon is then oxidatively removed from the tetrapyrrole ring, generating carbon monoxide and opening the ring structure, with oxygenation happening at the two nearby carbons. The cleavage results in equal amounts of biliverdin

and carbon monoxide. The carbon monoxide binds to hemoglobin and is eventually exhaled, while the removed α -carbon is also expelled as carbon monoxide, which acts as a neurotransmitter. The body recycles the iron released by heme oxygenase.

The resulting linear tetrapyrrole is biliverdin IX α , with the enzyme's stereospecificity leading to cleavage predominantly at the α -carbon of the tetrapyrrole. Subsequently, the central carbon atom (C-10) of biliverdin IX α undergoes reduction, changing from a methine group to a methylene group ($-\text{CH}_2-$), which results in the formation of bilirubin IX α . This reaction is facilitated by the enzyme biliverdin reductase located in the cytosol. Owing to the immediate availability and action of this enzyme, biliverdin seldom appears in the bloodstream. Thus, the bilirubin is esterified by glucuronosyl-transferase in the liver to monoglucuronosides and diglucuronosides, which are then excreted in the bile. The daily production rate of bilirubin is approximately 6–8 mg/kg in healthy term infants and 3–4 mg/kg in healthy adults [3,7].

3.2. Introduction of Stannoporphin (Tin mesoporphyrin)

Stannoporphin, also known as Tin mesoporphyrin (SnMP), is a synthetic metalloporphyrin that is a competitive inhibitor of heme oxygenase. It is currently being used clinically to treat hyperbilirubinemia [8].

3.2.1. SnMP and Its Role

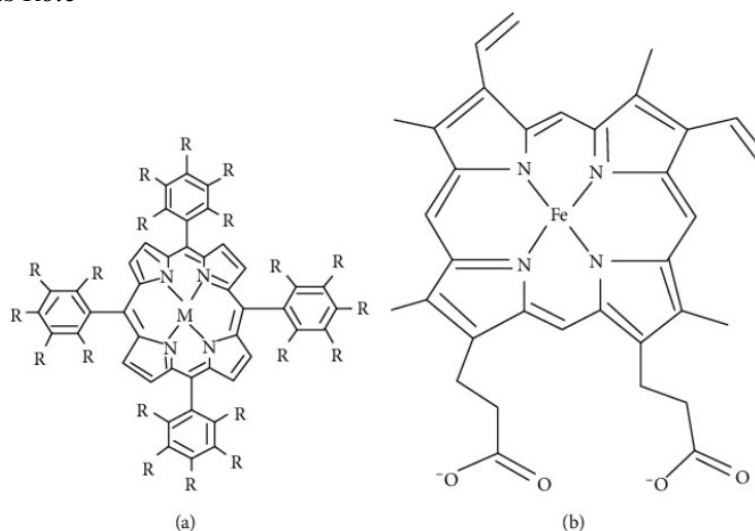


Figure 2. Metalloporphyrin. Adapted from Poudel and Adhikari.

Synthetic metalloporphyrins share a similar structure with natural heme, featuring a ring-structured protoporphyrin IX macrocycle. However, in synthetic metalloporphyrins, various metals—such as "tin (Sn), zinc (Zn), manganese (Mn), nickel (Ni), magnesium (Mg), copper (Cu), cadmium (Cd), cobalt (Co)"—replace the central iron (Fe) found in natural heme, as depicted in Fig. 2. Unlike heme, these synthetic metalloporphyrins cannot bind molecular oxygen and, therefore, are not degraded by the heme oxygenase (H.O.) enzyme. As a result, when these metalloporphyrins are present, heme cannot be broken down into biliverdin and, subsequently, bilirubin. Among the heme analogues that have been investigated, Tin protoporphyrin has been identified as a strong competitive inhibitor in the H.O. redox reaction [9].

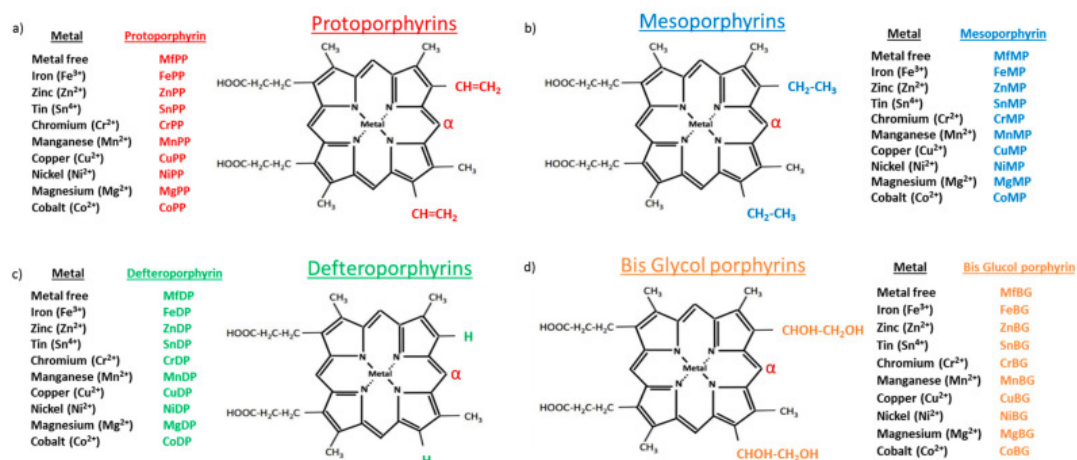


Figure 3. Metalloporphyrin (Mps) Types. Adapted from Lianos and Detsika.

The type of metalloporphyrin (Mp) that forms depends on the substitution of side chains on the porphyrin ring, leading to variations such as "protoporphyrins (P.P.), mesoporphyrins (M.P.), deuteroporphyrins (D.P.), and bis-glycol porphyrins (B.G.)," as shown in Fig. 3. These metalloporphyrins can either enhance or inhibit H.O. activity depending on the metal they contain; for example, FePP and cobalt protoporphyrin (CoPP) act as H.O. activators/inducers, while ZnPP, SnPP, and tin mesoporphyrin (SnMP) serve as H.O. activity inhibitors [4]. In addition to blocking heme metabolism in mammals, SnMP is also recognized for regulating tryptophan metabolism and accelerating the excretion of heme in mammals [10].

3.2.2. Chemical and Physical Properties of SnMP

Tin protoporphyrin (SnMP), also known as C₃₄H₃₆Cl₂N₄O₄Sn, is a small molecule with a molecular weight of 754.3 g/mol. Within the molecule is a flat structure; porphyrin rings show the sp² hybridization and a +4 oxidation state for the tin atom. The carbon atoms within the porphyrin ring are also sp² hybridized. Because of its stable structure, SnMP is relatively inert, and its stability makes it an effective competitive heme oxygenase inhibitor. The planar structure of the molecule and the specific hybridization state of its atoms play a crucial role in its binding affinity and inhibition [8,10,11].

Tin protoporphyrin showed lower solubility in water because of their hydrophobic porphyrin rings. However, SnMP chemical properties and solubility will change with the change in pH value. The solubility of SnMP is highly dependent on the pH of the solution, mainly because of its side chain propionate ionization and tin atom, which is the coordination liquid property. At high pH, "the chlorides eventually exchange with hydroxide ions" and form a highly soluble dihydroxide complex. In contrast, at "neutral pH, a monocoque-mono hydroxide complex exists in equilibrium with the other two species, and SnMP has an intermediate aqueous solubility at this pH." In acidic conditions, SnMP forms a poorly soluble complex [8].

3.2.3. Synthesis Method of SnMP

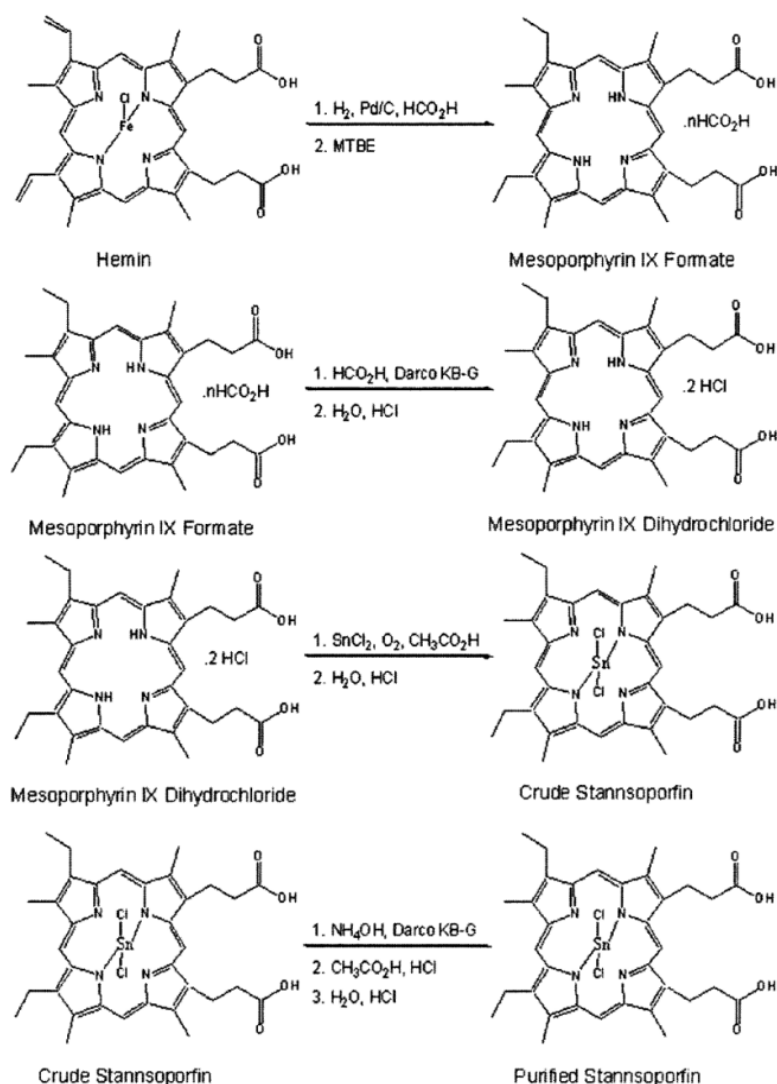


Figure 4. Methods for Synthesizing Tin Mesoporphyrin. Adapted from Boucher and Roe.

Tin protoporphyrin (SnMP), a potent competitive heme oxygenase inhibitor, has been synthesized by various methods. Each approach has advantages and disadvantages regarding purity, scalability, and efficiency. These methods can be divided into two main classes, starting with the natural porphyrin compound heme (Hemin) and starting with protoporphyrin IX: Fig. 4 shows the method starting with the natural porphyrin compound Hemin. (1) In this method, heme is first reduced by using hydrogen in the presence of a palladium/carbon (Pd/C) catalyst with methyl tert-butyl ether (MTBE) as the solvent, it was reduced to Mesoporphyrin IX Formate by converting the vinyl groups at C2 and C4 positions to ethyl groups [12]. Next, the methyl formate protoporphyrin IX was converted to Mesoporphyrin IX Dihydrochloride by reaction with formic acid and Darco KB-G, followed by hydrochloric acid treatment. This transformation step improves the solubility of the compound in subsequent reactions. The next step as a critical step is the insertion of tin ions into the porphyrin ring to form Crude Stannoporphin by treating the dihydrochloride protoporphyrin IX with tin chloride in the presence of oxygen and acetic acid. Finally, the crude tin protoporphyrin underwent a series of purification steps of ammonium hydroxide, Darco KB-G, acetic acid, and hydrochloric acid to yield highly purified tin

protoporphyrin suitable for clinical applications [12]. The main advantage of this method is the ability to produce SNMPS of high purity, which is essential for clinical applications that require extremely high product quality. However, this method involves many steps, is more complex, and takes time. At the same time, careful attention should be paid to the treatment and recovery of the palladium catalyst [12]. (2) An alternative synthesis method is to generate protoporphyrin methyl ester from heme, which is then converted to SnMP by metal insertion and hydrogenation. The advantage of this method is that the intermediate is relatively stable, which is suitable for environments where precise control of reaction conditions is required. However, handling the methyl ester intermediate may make the process more time-consuming and complex [12]. (3) An alternative method is to reduce heme to protoporphyrin IX intermediate without hydrogen, then insert tin, and finally hydrogenate when necessary. There is no need to worry about hydrogen treatment with this method. Although this approach may be more effective in some Settings, incomplete reduction may result in reduced purity [12]. (4) The protoporphyrin dihydrochloride IX intermediate method converts heme to a more soluble dihydrochloride form to facilitate the subsequent reaction and improve the efficiency of tin insertion. However, the required additional reagent and prolonged reaction time could limit its practicality in some environments [12]. (5) Finally, the single-step method for SnMP synthesis directly from heme is the simplest and most cost-effective method suitable for preliminary studies requiring rapid synthesis. However, this method may affect the purity of the final product, which may be a drawback in clinical applications [12]. (6) It is more convenient to synthesize protoporphyrin IX. This synthesis step is similar to the method starting from heme but is easier to perform because no deserialization is required. However, this approach may affect the purity of the final product, especially in applications where extremely high purity is required.

To conclude, there are multiple methods available for synthesizing SnMP, each offering different benefits and drawbacks regarding purity, scalability, and efficiency. The selection of the most suitable method depends on the specific needs of the application [12].

3.2.4. Mechanism of SnMP

Tin mesoporphyrin (SnMP) is a strong competitive inhibitor of heme oxygenase (H.O.), the enzyme responsible for breaking down heme into biliverdin, iron, and carbon monoxide [7].

A competitive inhibitor is any compound structurally resembling a particular substrate and competes with it for binding. While the enzyme does not act on the inhibitor, the inhibitor blocks the substrate from reaching the active site [13]. SnMP is structurally very similar to heme and, therefore, effectively competes with heme to bind to the active site of heme oxygenase. Once bound, SnMP inhibits the enzyme's activity, preventing it from breaking down heme [14].

Many metalloporphyrins can either inhibit H.O. or induce H.O., and SnMP is a good choice. In a study examining the effects of various metalloporphyrins on heme metabolism in adult male rats, Sn-heme, Mn-heme, and Zn-heme were found to significantly reduce hepatic heme oxygenase activity by 50-60% when administered at a dose of 50 $\mu\text{mol/kg}$ body weight. Conversely, Cd-heme, Fe-heme, and Co-heme increased heme oxygenase activity by 100-400%, while other metalloporphyrins had little effect. When Sn-heme was administered at 125 $\mu\text{mol/kg}$, it inhibited δ -aminolevulinate synthase activity by 60% [15].

Functional groups in SnMP play a crucial role in its inhibition: (1) The porphyrin ring system is a chelator that binds the central tin (IV) ion. The (2) tin ion occupies the active site of H.O. and plays a key role in inhibiting it. The (3) propionic acid side chain ($-\text{CH}_2\text{CH}_2\text{COOH}$) enhances the binding affinity and specificity of the molecule to the enzyme; the (4) ethyl ($-\text{CH}_2\text{CH}_3$) formed during synthesis raises the stability of SnMP. In addition, the (5) carbonyl group ($=\text{O}$), part of the conjugated system in the porphyrin ring, influences the electronic properties and overall reactivity of the ring.

While Sn-heme and Sn (Tin) mesoporphyrin are distinct compounds, their similar mechanisms in inhibiting heme oxygenase underscore the therapeutic potential of tin-substituted porphyrins in managing hyperbilirubinemia.

Table 1. Effect of Metalloporphyrins on Heme Oxygenase and δ -aminolevulinate Synthase Activities in Liver. Adapted from Drummond and Kappas.

Metalloporphyrin	Heme Oxygenase, nmol bilirubin/mg protein per hr	δ -Aminolevulinate Synthase, nmol aminolevulinate/mg protein per hr	In Vivo Bilirubin Reduction
Control	2.47 $\pm$ 0.12	0.178 $\pm$ 0.01	N/A
Manganese	1.05 $\pm$ 0.16*	0.068 $\pm$ 0.01*	Significant
Zinc	1.24 $\pm$ 0.14*	0.098 $\pm$ 0.01*	Moderate
Tin	1.08 $\pm$ 0.13*	0.177 $\pm$ 0.04	High
Copper	2.82 $\pm$ 0.10	0.198 $\pm$ 0.01	Low
Nickel	3.70 $\pm$ 0.46	0.110 $\pm$ 0.01*	Low
Magnesium	3.65 $\pm$ 0.68	0.043 $\pm$ 0.01*	Moderate
Cadmium (Cd)	5.26 $\pm$ 0.50*	0.025 $\pm$ 0.01*	Low
Iron	6.50 $\pm$ 0.59*	0.040 $\pm$ 0.01*	Moderate
Cobalt	10.92 $\pm$ 0.79*	0.108 $\pm$ 0.01*	Low

*Metalloporphyrins were administered subcutaneously in a single dose (50 μ mol/kg body weight) to the animals, which were killed 16 hr later. Three to six animals were used for each determination, and the assays were duplicated. Data are presented as mean $\pm$ SEM. *P < 0.05, compared with control.

Although Manganese and tin metalloporphyrins have the highest reduction of H.O. compared to the control group shown in Table 1, tin has a minimal effect on δ -synthetase activity, directly reducing bilirubin production without seriously disrupting heme synthesis. Also, Sn-heme selectively inhibits bilirubin production, is stable, and has documented clinical efficacy. There is less clinical evidence to support using magnesium porphyrins for this purpose. In addition to tin metalloporphyrins, another used to inhibit heme oxygenase is zinc protoporphyrin (ZnPP), which also has its advantages. Zinc protoporphyrin is also effective in inhibiting H.O. activity and has been studied for lowering bilirubin levels. However, while both SnMP and ZnPP inhibit heme oxygenase, their mechanisms of action are quite different. SnMP is particularly noted for reducing both HO-1 expression and activity [16], whereas ZnPP primarily inhibits activity and can sometimes induce HO-1 expression [17]. This makes SnMP potentially more effective for sustained reduction of bilirubin levels.

3.2.5. Metabolism

Although the solubility of the SnMP under high pH increased due to its hydrophobicity of porphyrin ring structure, it is still not easy to dissolve in nature. Formulation forms of lyophilized liposomes are typically used to deliver SNMPS and prevent their degradation [8] efficiently. Liposomes are tiny, man-made spherical vesicles composed of cholesterol and naturally occurring, non-toxic phospholipids [18].

After injection, the lipid is experienced through the blood circulation and by the liver and spleen of reticuloendothelial system (RES) absorption. In these organs, liposomes release SnMP, which inhibits heme oxygenase and reduces bilirubin production. It has been shown that "the distribution of liposomal SnMP to spleen at 2 and 6 hr after dosing was 5-20 times higher than for aqueous SnMP." The liposomal form of SnMP was shown to be more effective in reducing bilirubin production than its aqueous form [8].

SnMP is excreted primarily via the biliary route. "Tin-mesoporphyrin is cleared from the plasma of normal subjects with dose-dependent pharmacokinetics ($T_{1/2}$ = 3.8 hr following i.v. administration of 1 μ mole per kg body weight), and small amounts (less than 1% of administered dose) are excreted into the urine and feces" [19]. SnMP liposomes are typically prepared by "high-pressure homogenization of a suspension of SnMP and egg phosphatidylcholine in lactose-phosphate buffer," resulting in "liposomes that were less than 200 nm in diameter and had encapsulation efficiencies of

up to 90% at pH 5" [8]. After freeze-drying, these liposomes have a longer shelf life, which is more suitable for long-term storage and injection.

3.2.6. *Side Effects of SnMP*

Tin protoporphyrin (SnMP) has proved effective in treating high bilirubin hematic disease, especially in reducing phototherapy demand, which has a significant effect. Much research on human babies suggests that SnMP can effectively control the bilirubin level, reducing the demand for phototherapy.

Although SnMP has a good effect in treating hyperbilirubinemia, its use is also accompanied by certain risks. First, the compound with light toxicity "contains a foreign metal that may be released," which may induce the heme oxygenase (H.O.) expression. It may also inhibit other essential enzymes, such as nitric oxide synthase and soluble guanylate cyclase acid, the product of these enzymes plays a crucial role in critical biological functions. Therefore, SnMP has not been widely used to treat high blood bilirubin. Despite this, "bloodless medicine" advocates are still promoting its use to avoid exchange transfusion requirements [20]. In addition, using SnMP was also associated with the risk of iron deficiency anemia. This is because SnMP, while inhibiting H.O. activity, may also affect the recycling and utilization of iron in the body, resulting in iron deficiency.

SnMP is a potent in vitro and in vivo photosensitizer, which makes photosensitization-induced cytotoxicity a significant concern. Photosensitization involves the generation of free radicals or singlet oxygen species that can react with the biological matrix, resulting in membrane damage and, eventually, cell death, usually through accelerated lipid peroxidation and changes in proteins and nucleic acids [21]. SnMP light toxicity can be attributed to the porphyrin structure, making it when exposed to light with photosensitive toxicity [22].

However, studies have shown that the phototoxicity of SnMP can be controlled under specific conditions. SnMP exhibited phototoxicity only at high doses when irradiated using A phototherapy lamp emitting UV A light. However, SnMP was not phototoxic when A phototherapy lamp that did not emit UV A light was used. In all cases, the phototoxic effects were reversible once the drug and phototherapy treatment were stopped [23]. In addition, the study also showed that SnPP under the lowest dose had mild light toxicity, and SnMP only at the highest doses showed light toxicity. The light toxicity was reversible [23].

3.2.7. *History of SnMP*

Attallah Kappas, a professor emeritus at Rockefeller University and former physician-in-chief at Rockefeller University Hospital, significantly contributed to the development of SnMP during the 1980s [24]. To find safer and more effective treatments for neonatal jaundice and other related conditions, Dr. Kappas experimentally investigated the effects of various metalloporphyrins on heme metabolism in adult male rats. His studies ultimately determined that tin was the most effective and safest choice of the metal porphyrins tested [15].

3.3. *Compare SnMP to Other Hyperbilirubinemia Treatments*

Currently, there are four treatments for hyperbilirubinemia, including phototherapy, exchange transfusion, drug therapy (such as tin protoporphyrin SnMP), and intravenous immunoglobulin (IVIg). Phototherapy is indicated for mild cases and is safe and effective, but requires constant exposure to light and may cause dehydration, rash, and body temperature instability. For severe cases, the change effectively reduces bilirubin levels in the blood, but it belongs to invasive procedures, such as infections and thrombosis risk. In addition, both phototherapy and exchange transfusion are attempts to eliminate bilirubin after it has already formed and reached dangerous levels in the blood of the newborn. By this time, however, bilirubin may already pose a toxic threat to the nervous system. To address this problem, Attallah Kappas and his research team developed heme oxygenase inhibitors, including SnMP, designed to block bilirubin production at an early clinical stage and prevent it from reaching harmful levels in the blood. Such an inhibitor "should have pharmacologic and toxicological properties suitable for clinical use in human neonates to prevent severe hyperbilirubinemia and thereby

eliminate practical concerns about the problem of bilirubin-induced brain damage” [25]. SnMP has light toxicity; however, it needs to avoid light strictly and has not yet been approved for clinical use. Intravenous immunoglobulin (IVIg) is another option, especially suitable for immune-mediated jaundice because it can reduce cause hemolytic antibody levels. However, it is expensive and not effective for all forms of jaundice [26]. Each treatment has advantages and disadvantages, and treatment choices depend on the severity of the condition, the underlying cause, and the patient's specific needs.

4. Conclusion

Tin protoporphyrin (SnMP) provides a promising alternative to the traditional treatment of hyperbilirubinemia by inhibiting heme oxygenase and preventing the formation of bilirubin. Although phototherapy and exchange transfusion are currently effective, they are often performed after the bilirubin has already accumulated to dangerous levels. At the same time, SnMP provides a preventive treatment strategy, reducing the use of invasive treatment methods and providing patients with short-term effective relief. However, although SnMP shows some efficacy, it has its challenges. Its light toxicity and could cause side effects, such as iron deficiency anemia, still needs further research and careful evaluation, and can be widely used in clinics. SnMP synthesis method through a variety of optimization, each method on the purity, scalability, and efficiency are trade-offs. Continued research on SnMP and its comparison with other metal porphyrins, such as ZnPP, will play a great role in treating neonatal hyperbilirubinemia. As clinical trials progress, SnMP can be approved for widespread use as a safer and more aggressive treatment option.

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