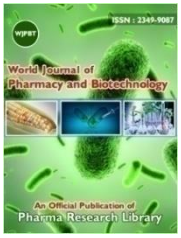

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Review on Phocomelia

Dilshad Khaddar, M. Joshna*, Vagga. Shireesha, Nesa Swathi, Abburi Anil Kumar, Chilapam Uday, Reddy Sai Shashank, Shaik Furquan Ahmed, M.S Harsha Vardhan Reddy
Saastra College of Pharmaceutical Education & Research, Varigonda, Totapalligudur, Nellore, Andhra Pradesh-524311

A B S T R A C T
This study focuses on the development and evaluation of controlled-release (CR) tablets of Sotagliflozin, an anti-diabetic drug. A calibration curve in 6.8 phosphate buffer showed linearity in the 2-10 µg/ml range, with a regression coefficient of 0.999. Pre-compression assessments, including Carr's index (≤ 18), Hausner's ratio (1.09-1.21), and angle of repose (22.17-31.11°), indicated good flow properties. Post-compression results showed tablet weights from 498.0 to 502.2 mg, thicknesses between 5.82 and 5.91 mm, hardness values from 5.9 to 6.3 kg/cm², and friability below 1%, indicating robust tablets. Drug content was within the 98-102% range. In vitro dissolution studies, conducted using a USPType2 apparatus in 6.8 sodium phosphate buffer, demonstrated over 99% drug release within 12hours, with release rates depending on polymer composition. FTIR analysis confirmed the absence of significant interactions among Sotagliflozin, HPMC, and Sodium Alginate. The findings suggest that Sotagliflozin CR tablets possess suitable physicochemical properties and effective release profiles for diabetes management.

Keywords: Sotagliflozin, HPMC, Sodium Alginate, Carr's index, Hausner's ratio

A R T I C L E I N F O

***Corresponding Author:**	**Article History:**
M. Joshna	**Received** 07 Oct 2024
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C O N T E N T S

1. Introduction

Phocomelia is a devastating, rare congenital limb malformation in which the long bones are shorter than normal, with the upper portion of the limb being most severely affected. In extreme cases, the hands or fingers are attached directly to the shoulder and the most proximal elements (those closest to the shoulder) are entirely missing. This disorder, previously known in both autosomal recessive and sporadic forms, showed a marked increase in incidence in the early 1960s due to the tragic toxicological effects of the drug thalidomide, which had been prescribed as a mild sedative.1

Phocomelia is a congenital condition that involves malformations of human arms and legs which result in a flipper like appendage. A prominent cause of phocomelia is the mother being prescribed the use of the drug thalidomide during pregnancy; however, the causes of most cases are to be determined. Occurrence in an individual results in various abnormalities to the face, limbs, ears, nose, vessels and many other underdevelopments. Although operations may improve some abnormalities, many are not surgically treatable due to the lack of nerves and other related structures.

Figure.1

Phocomelia is an extremely rare congenital disorder involving malformation of the limbs (dysmelia). Étienne Geoffroy Saint-Hilaire coined the term in 1836.[3]

Figure.2

Etiology:

Phocomelia is a rare congenital with various etiologies. Here are some possible causes:

Genetic factors:

1. Autosomal recessive inheritance
2. Chromosomal abnormalities (e.g., trisomy 13, 18)
3. Genetic mutations (e.g., HOXD13, WNT5A)
4. Familial phocomelia

ENVIRONMENTAL FACTORS:

1. Thalidomide exposure (historical, 1950s-1960s)
2. Maternal smoking
3. Exposure to toxic substances (e.g., pesticides, heavy metals)
4. Infections during pregnancy (e.g., Zika virus, rubella)
5. Radiation exposure

Teratogenic agents:

1. Thalidimide
2. Alcohol
3. Cocaine
4. Anticonvulsants (e.g., valproic acid)
5. Warfarin

INFECTIONS:

1. Zika virus
2. Rubella
3. Cytomegalovirus
4. Toxoplasmosis

OTHER FACTORS:

1. Advanced maternal age
2. Diabetes during pregnancy
3. Obesity
4. Hypertension
5. Trauma during pregnancy.

2. Causes

Main cause of phocomelia is drug called thalidomide:

Thalidomide released on to market in 1958 in West Germany under the name contergan. Primarily prescribed as a sedative and hypnotic, thalidomide also claimed to cure anxiety, insomnia, gastritis and tension. Afterwards it was used against Nausea and to alleviate Morning Sickness in pregnant women. Thalidomide became an over-the-counter drug in Germany around 1960, i.e. it could be bought without a prescription. Shortly after the drug was sold, in Germany between 5,000 and 7,000 infants were born with phocomelia. Only 40% of these children survived.

Research also proves that although phocomelia did exist through the 1940s and 1950s, cases of severe phocomelia multiplied in the 1960s when thalidomide was released in Germany; the direct cause was traced to thalidomide. The statistic was given that "50 percent of the mothers with deformed children had taken thalidomide during the first trimester of pregnancy." Throughout Europe, Australia, and the United States, 10,000 cases were reported of infants with phocomelia; only 50% of the 10,000 survived. Thalidomide became effectively linked to death or severe disabilities among babies. Those subjected to thalidomide while in the womb experienced limb deficiencies in that the long limbs either were not developed or presented themselves as stumps. Other effects included deformed eyes, hearts, alimentary and urinary tracts, blindness and deafness.

Genetic inheritance:

According to the National Organization for Rare Disorders (NORD), when phocomelia is transmitted (in its familial genetic form) it is seen as an autosomal recessive trait and the mutation is linked to chromosome 8. A study of Roberts syndrome, a genetic disorder showing similar symptoms to phocomelia, has shed light on the possible causes. An individual afflicted with Roberts Syndrome will have chromosome copies that do not connect at the centromeres, making them unable to line up accordingly. As a result, the newly made cells contain an excess or reduced number of chromosomes. In both Roberts syndrome and phocomelia the cells cease to develop, or die, preventing proper development of the limbs, eyes, brain, palate, or other structures

Thalidomide syndrome symptoms:

When an individual is born with phocomelia due to drugs or pharmaceuticals, it is known as thalidomide syndrome. The symptoms of thalidomide syndrome are defined by absent or shortened limbs, causing flipper hands and feet. According to Anthony J Perri III and Sylvia Hsu they can additionally receive:

Palsy disorder of the face

Ear and eye abnormalities, resulting in limited/complete loss of hearing or sight

Gastro intestinal and Genitourinary tract disorders

In grown genitalia

Undeveloped/missing lungs

Distorted digestive tract, heart, kidney

Hypoplastic or absent bones

The infants that were exposed to thalidomide during development phases had a 40% chance of survival. The Mc Credie–Mc Bride hypothesis explains that the limbs of the infants become malformed as a result of the thalidomide harming the neural tissue—simply because the neural tissue has such a large impact on formation and development of the limbs.

3. Treatment

Prosthesis is a synthetic alternative for missing limbs, teeth, and various other body parts. Advances in materials, pigments and manufacturing methods during the twentieth century have rendered artificial limbs lighter in weight and more realistic-looking. Myoelectric prostheses take all their input from the nervous system and muscles at the site of attachment in the form of electric signals.

Children born with phocomelia are recommended to have a prosthetic mitten fitted to get used to the sensation of wearing an aid early on; typically a hook is added around the age of two years until the necessary tissues, bone structures, proprioception and motor coordination have developed to permit use of a myoelectric prosthetic limb

Notable cases:

Matthias Buchinger (1674 - 1740) was born without hands or legs and was an artist and performer who travelled across Northern Europe. Despite his handicap Buchinger was an incredibly accomplished micro-engraver, magician, marksman, musician. He was married 4 times and had 14 children.

Louis Joseph César Ducornet, (1806 – 1856) was a French painter who painted with his foot. He is known primarily for biblical and historical scenes, as well as portraits. Ame Barnbrook was born without arms and only the lower half of her left leg, and three toes. She has a rarer form of phocomelia, meaning all of her limbs are affected. She graduated from the University of Wollongong with a Bachelor of Creative Arts. Barnbrook plays the trumpet with her foot and is a competitive sailor.[14] She sails a SKUD18 at world championship level. She did not qualify for the 2012 Paralympic Games in London, but she trained for the 2016 Paralympic Games in Rio de Janeiro.

Sarah Biffen (c. 1784 – 1850), was an English painter born without arms and only vestigial legs. She learnt to paint by mouth, was taught by William Craig, and exhibited at the Royal Academy. Biffen was commissioned to paint miniatures of the Royal Family, and Queen Victoria later awarded her pension.

Eli Bowen, who made his living performing in sideshows. Mat Fraser was born with phocomelia due to his mother taking thalidomide while she was pregnant. He is known as the drummer of rock bands including Fear of Sex, The Reasonable Strollers, Joyride, The Grateful Dub, and Living in Texas. He is also an actor and performing artist. Rahma Haruna was born in Nigeria with severe phocomelia. She had no limbs, except for a partially formed right hand that was attached to her axilla. Rahma's story came out when a local journalist saw her on the street with her brother, after which the story was shared widely on social media. She died at the age of 19, on 25 December 2016.

Hee Ah Lee, a pianist who has two fingers on each hand. Alison Lapper was born with phocomelia. She is arm deficient and has shortened bones and legs. Lapper graduated from Brighton University in 1994, established herself as a visual artist, and in 2000 gave birth to a son, Parys. Lapper produces cards and calendars for The Mouth and Foot Painters' Association. She does not wear prosthetic limbs.

Figure.3. Global Cases of Phocomelia

Genetic Inheritance

According to NORD, when phocomelia is transmitted (in its familial genetic form) it is seen as an autosomal recessive trait and the mutation is linked to chromosome 8.2,4 There are several attachment points in a chromosome, the centromere is the major connection point and where the immensity of the work generates. An individual containing phocomelia will have chromosome copies that do not connect at the centromeres, making them unable to line up accordingly. As a result, the cell becomes incapable of division or slow in the process; because of this the newly made cells contain an excessive or reduced amount of chromosomes.2,11 In phocomelia the cells cease to develop, or die, preventing proper development of the limbs, eyes, brain, palate, or other structures.

Discussion

The first case of phocomelia was described in Germany in 1956. Father of the child was working as a pharmacist, mother had received thalidomide for nausea of pregnancy. After delivery baby was found to have had no arms and only vestigial flipper like hands. Thalidomide was released into market in 1957 in West Germany. Initially, it was used as a sedative or hypnotic, thalidomide also claimed to cure anxiety, insomnia, gastritis and tension.2,6 Later it was used to combat against nausea and alleviate morning sickness in pregnant women. Thalidomide became an over the counter drug in Germany around 1960, and could be purchased without a prescription. Shortly after the drug's selling, in Germany, between 5,000 and 7,000 infants were

born with the qualities of phocomelia.2,7 Out of these children merely 40% of them survived.

Figure.4. Underdeveloped upper limbs with fused fingers

Figure.5. Short lower limb with polydactyly and fused toes

4. Conclusion

Most of the anomalies can be diagnosed antenatally if we do the anomaly scan at around 18 to 20 weeks of gestation. Hence, we should ask all the pregnant mothers to have at least one USG at 18 to 20 weeks to rule out any anomalies in the baby. We have asked the patient and relatives to take folic acid preconceptionally, regular antenatal visit is must. We have advised triple test or amniocentesis in next pregnancy, routine diabetes screening to rule out other congenital anomalies. Since phocomelia is diagonsed with USG, we can do anomaly scan at early second trimester

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