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Review Article

Mitapivat: An Overview

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Abstract

Mitapivat is used to treat hemolytic anemia (a condition in which more red blood cells are destroyed than made into the body) in people with pyruvate kinase deficiency. Mitapivat is in a class of drugs called pyruvate kinase activators .mitapivat increases pyruvate kinase which results in increment in lifespan of red blood cells. Mitapivat comes as a tablet which is taken orally. It's generally taken with or without food 2 times a day. Mitapivat is taken around the same times every day. Patient should Follow the directions on prescription label precisely. It should not be taken more, less or take it or more frequently than specified by the doctor.

Keywords: Mitapivat, Hemolytic, Red Blood cells, Patient.

Introduction

Mitapivat is a small molecule inhibitor being delved for the treatment of various hematologic diseases, including pyruvate kinase insufficiency(PKD) and sickle cell complaint(SCD). It works by targeting the allosteric list point of pyruvate kinase- R(PK- R), an enzyme involved in red blood cell metabolism

Mitapivat controls hemolytic anemia from pyruvate kinase insufficiency but doesn't cure it. Mitapivat shouldn't be stopped without consulting doctor..However, If mitapivat is stopped suddenly symptoms like acute hemolysis and anemia (yellowing of the skin or whites of the eyes) is seen .Its dosagege should. be dropped gradationally.[1]

Pyruavate Kinase Deficiency Anaemia

Pyruvate kinase is an enzyme that helps cells turn sugar(glucose) into energy(called adenosine triphosphate, ATP) in a process called glycolysis. Red cells use on this process for energy, and so, pyruvate kinase deficiency leads to a insufficiency in energy and red cell destruction(hemolysis). PKD is inherited in an autosomal recessive manner, meaning both parents must carry a copy of the mutated gene for a child to develop the condition. The disease can result from mutations in the PKLR gene, which provides instructions for producing PK-R (red cell-specific pyruvate kinase) enzyme. Without sufficient PK activity, red blood cells have a shorter lifespan and are more prone to destruction. [2]

Cause

Pyruvate kinase deficiency PKD) is a rare inheritable disorder characterized by a insufficiency or dysfunction of the enzyme pyruvate kinase(PK). PK is an important enzyme involved in the final step of glycolysis(the process by which cells produce energy from glucose). PK catalyzes the conversion of

phosphoenolpyruvate(vim) to pyruvate, generating ATP(adenosine triphosphate) in the process. [3] PKD leads to a reduced production of PK, which impairs the metabolism of red blood cells(RBCs) and causes hemolytic anemia. Haemolytic anaemia is a type of anaemia in when RBCs break down more quickly than they can be replaced, resulting in a shortage of functional red blood cells. [4]

Signs and symptoms [5]

This desease can affect a variety of population. Majorly those suffering from pyruvate kinase deficiency are detected at birth or when body undergoes major physiological changes such as pregnancy.

Some symptoms include-

- Mild to severe hemolytic Anemia
- Cholecystolithiasis
- Tachycardia
- Hemochromatosis
- Icteric sclera
- Splenomegaly
- Leg ulcers
- Jaundice
- Fatigue
- breathless ness

Diagnosis

The opinion of PKD involves many laboratory tests, including measuring PK enzyme production, genetic testing to identify mutations in the PKLR gene, and assessing red blood cell characteristics. Treatment options for PKD are substantially probative and aim to manage symptoms. This may include blood transfusions, folic acid supplementation, and, in severe cases, splenectomy(surgical junking of the spleen). [6]

TREATMENT [7, 8**]**

Most individuals with pyruvate kinase deficiency do not require treatment. However, in severe cases, the disease can be life-threatening, leading to anemia in utero or requiring intensive treatment. While there is no cure for pyruvate kinase deficiency, treatment options are available and can effectively reduce the severity of symptoms. Blood transfusions, particularly in infants and young children, are the most common treatment when the red blood cell count falls to a critical level. In some cases, bone marrow transplantation has been conducted as a treatment option.

The body naturally increases erythrocyte production (reticulocytosis) as a way to combat the disease. Reticulocytes, which are immature red blood cells containing mitochondria, can produce ATP through oxidative phosphorylation. In extremely severe cases, a splenectomy may be performed to increase the amount of reticulocytes in the body. Although it does not stop erythrocyte destruction, it reduces anemia and the need for blood transfusions by preventing the trapping of reticulocytes in the hypoxic environment of the spleen.

Mitapivat, a medication approved for medical use in the United States in February 2022, offers another treatment option for pyruvate kinase deficiency.

Pharmacology of Mitapivat

Brand Names- Pyrukynd 5 Mg 4-week

Generic Name -Mitapivat

Background

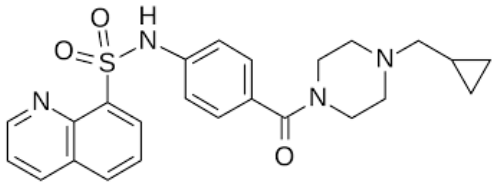
Mitapivat is an innovative pyruvate kinase activator, representing a unique class of drugs. Its mechanism of action involves enhancing the activity of erythrocyte pyruvate kinase, a crucial enzyme responsible for the survival of red blood cells. Various disorders affecting the pyruvate kinase enzyme can result in inadequate energy production for red blood cells, leading to the lifelong premature destruction of these cells or chronic hemolytic anemia [9].

The significant breakthrough came on February 17, 2022, when the FDA granted approval to mitapivat as the first disease-modifying therapy for hemolytic anemia in adult patients diagnosed with pyruvate kinase (PK) deficiency. PK deficiency is an inherited disorder characterized by lifelong hemolytic anemia, and mitapivat marks a significant advancement in its treatment [16]. Additionally, researchers have explored the potential of mitapivat in addressing other hereditary red blood cell disorders associated with hemolytic

anemia, including sickle cell disease, alpha-thalassemia, and beta-thalassemia [9].

Type - Small Molecule

Structure



N-[4-[4-(cyclopropylmethyl)piperazine-1-carbonyl]phenyl]quinoline-8-sulfonamide;sulfuric acid;trihydrate [10]

Average weight : 450.56

Chemical Formula- C24H26N4O3S

Indication

Mitapivat is used for treatment of haemolytic anaemia which is cause by pyru vate kinase deficiency.

Pharmacodynamics

Mitapivat is a compound that acts as a pyruvate kinase activator, promoting increased activity of erythrocyte pyruvate kinase. This enzyme plays a crucial role in the production of energy and the survival of red blood cells. It is effective in enhancing the activity of both wild-type and mutant forms of erythrocyte pyruvate kinase [9,15].

An intriguing characteristic of mitapivat is its ability to mildly to moderately inhibit the aromatase enzyme (CYP19A1) [9]. Aromatase is involved in the synthesis of estrogens from androgen precursors. Inhibiting this enzyme can impact bone density because estrogen exerts suppressive and antiresorptive effects on osteoclasts, favoring bone formation over resorption. When estrogen levels are low, bone turnover and osteoclast activity may increase, leading to a net loss of bone and decreased bone quality [10]. Since individuals with pyruvate kinase deficiency often have a higher prevalence of osteopenia and osteoporosis, it is important to further investigate the long-term effects of mitapivat on bone mineral density. While one study suggests that the off-target effect of aromatase inhibition by mitapivat may have minimal clinical significance in adults, it could potentially have implications in developing children [9].

Mechanism of action

The pyruvate kinase enzyme is a vital component of the Embden-Meyerhof glycolytic pathway, responsible for generating ATP. In the final step of glycolysis, it catalyzes the conversion of phosphoenolpyruvate to pyruvate, producing adenosine triphosphate (ATP) essential for cellular function and survival. Among the different isoforms of pyruvate kinase, erythrocyte pyruvate kinase (PKR) specifically operates in red blood cells (RBCs). Unlike most human cells, RBCs lack the necessary metabolic mechanisms for aerobic glucose metabolism and ATP generation, relying on anaerobic glycolysis as their primary source of ATP production. Defects in glycolytic enzymes and the resulting ATP deficiency lead to the shortened lifespan and premature destruction of RBCs, manifesting as chronic hemolytic anemia and ineffective erythropoiesis [9].

Pyruvate kinase deficiency is an uncommon inherited disorder affecting RBC glycolysis, caused by mutations in the PKLR gene. This gene encodes both the RBC-specific isoform (PKR) and the liver-specific isoform (PKL) of pyruvate kinase. Pyruvate kinase deficiency is associated with elevated levels of 2,3-disphosphoglycerate (2,3-DPG), an intermediary metabolite in glycolysis, as well as reduced ATP levels [14].

Erythrocyte pyruvate kinase is an enzyme that functions as a homotetramer and is regulated through allosteric mechanisms. Its activation is typically achieved by fructose bisphosphate (FBP) binding to an allosteric site. However, mitapivat, an allosteric pyruvate kinase activator, interacts with a distinct allosteric site on the PKR tetramer, separate from the FBP binding site. This unique binding mechanism enables the activation of both wild-type and mutant forms of erythrocyte

pyruvate kinase, including those not responsive to FBP induction [9, 15].

When mitapivat binds to pyruvate kinase, it stabilizes the active tetrameric configuration of the enzyme and enhances its affinity for the substrate, phosphoenolpyruvate [13]. This results in an upregulation of erythrocyte pyruvate kinase activity, leading to increased ATP production and a decrease in the levels of 2,3-disphosphoglycerate (2,3-DPG) [9, 15].

Absorption

The absolute bioavailability of mitapivat is approximately 73% following a single dose. The exposure to mitapivat increases proportionally with the dose administered. When mitapivat is administered orally twice daily at doses of 5 mg, 20 mg, and 50 mg, the mean (CV%) maximum concentration (Cmax) at steady state is 101.2 (17%) ng/mL, 389.9 (18%) ng/mL, and 935.2 (18%) ng/mL, respectively. The mean (CV%) area under the concentration-time curve (AUC) is 450.4 (28%) ng x h/mL, 1623.8 (28%) ng x h/mL, and 3591.4 (28%) ng x h/mL, respectively. The median time to reach maximum concentration (Tmax) at steady state ranges from 0.5 to 1.0 hour post-dose across the dose range of 5 mg to 50 mg twice daily [15].

In healthy subjects, the consumption of a high-fat meal does not significantly affect the exposure to mitapivat but results in a reduction of the rate of absorption. This reduction is characterized by a 42% decrease in Cmax and a delay in Tmax of approximately 2.3 hours compared to administration under fasted conditions.

Volume of distribution

At steady state the mean volume of distribution (Vss) was 42.5 L.(15)

Protein binding

Mitapivat is 97.7% bound to plasma proteins, with an RBC-to-plasma ratio of 0.37.(15)

Metabolism

Mtapivat is metabolised in liver with the help of cytochromes. According to in vitro studies, it is mainly metabolized by CYP3A4 and CYP3A5. It is also a substrate of CYP1A2, CYP2C8, and CYP2C9.[15]

Route of elimination

Mitapivat is eliminated primarily by hepatic metabolism.

Renal excretion involves the filtration of the drug and its metabolites through the glomerulus, followed by subsequent reabsorption or active secretion in the renal tubules.

It is worth noting that the route of elimination can be influenced by various factors, such as individual patient characteristics, drug interactions, and any underlying medical conditions. For accurate and up-to-date information on the specific elimination pathway of mitapivat, it is best to consult the prescribing information, package insert, or consult with a healthcare professional or pharmacist. [16]

Half-life

In pyruvate kinase deficiency patients who are receiving doses of 5 to 20 mg twice daily, the mean effective half-life (t1/2) of mitapivat ranges from 3 to 5 hours.(15)

Clearance

derived median CL/F of Population pharmacokinetics at steady state is 11.5, 12.7, and 14.4 L/h for the 5 mg twice daily, 20 mg twice daily, and 50 mg twice daily regimens. [15]

Pharmacogenomic Effects/ADRs

Mitapivat, like any medication, may have adverse drug reactions (ADRs) that can occur during treatment. Some of the known ADRs associated with Mitapivat include:

1. Headache
2. Fatigue
3. Nausea
4. Diarrhea
5. Abdominal pain
6. Decreased appetite
7. Muscle spasms
8. Dizziness
9. Insomnia
10. Upper respiratory tract infection

Drug Interactions [17]

•Abacavir: The metabolism of Abacavir may be increased when combined with Mitapivat.

•Abametapir: The serum concentration of Mitapivat may be increased when combined with Abametapir.
•Abemaciclib: The metabolism of Abemaciclib may be increased when combined with Mitapivat.
•Acalabrutinib: The metabolism of Acalabrutinib may be increased when combined with Mitapivat.
•Acarbose: The therapeutic efficacy of Acarbose may be increased when used in combination with Mitapivat.
•Acenocoumarol: The metabolism of Acenocoumarol may be increased when combined with Mitapivat.
•Acetaminophen: The metabolism of Acetaminophen may be increased when combined with Mitapivat.
•Acetohexamide: The therapeutic efficacy of Acetohexamide may be increased when used in combination with Mitapivat.
•Afatinib: The serum concentration of Afatinib may be increased when combined with Mitapivat.
Albendazole: The metabolism of Albendazole may be increased when combined with Mitapivat

Food Interactions

•Take with or without food. Food has a negligible effect on the exposure of mitapivat, but may reduce the rate of drug absorption, Cmax, and Tmax

Side effects [18]

•Back pain
•Joint pain
•Nausea, vomiting, diarrhea or stomach pain
•Hot flushes (warmth and redness of face, neck, chest or back)
•Sore throat
•Breast pain or swelling
•Constipation
•Dry mouth
•Rapid or fast heart beat
•Tingling feeling in hands, arms, feet or legs

Conclusion

Mitapivat is a small molecule drug. It is FDA approved drug which is used to treat PK deficiency, a rare, inherited blood disorder that may cause blood cell destruction. Overall, mitapivat shows potential as a novel therapeutic option for patients with PKD and other related disorders. However, it is essential to consult with healthcare professionals and closely follow the latest scientific and regulatory updates for the most accurate and up-to-date information on mitapivat.

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