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PHARMACOKINETICS OF DEFERASIROX FILM COATED TABLET (JADENU)IN PEDIATRIC PATIENTS

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Thalassemia is a hereditary blood disorder which is caused by mutation of either alpha (α) or beta (β)globin gene which results in defective hemoglobin synthesis. Thalassemia can be classified based on genotypic diagnosis into two groups: α-thalassemia and β-thalassemia. They can also be categorized based on the clinical degree of severities into three types: thalassemia major, intermedia, and minor. β-thalassemia major (β-TM) is the **Etiology**

Thalassemia is directly linked to genetics and how the genes that affect haemoglobin production are inherited. People with moderate to severe forms received variant genes from both parents. People who are carriers of the disease received variant genes from one parent and normal genes from the other parent **(Galanello and Origa, 2010).**

Classification:

The thalassemia syndrome is classified according to which of the globin chains, α or β, is affected. These 2 major groups, α and β-thalassemia, are sub classified according to absent (αo and βo) or reduced (α+ or β+) globin chain synthesis **(Leitch, 2016)**.There are two primary types of thalassemia disease: Alpha thalassemia disease and beta thalassemia disease. Beta thalassemia Major (cooley's Anemia) is a serious illness, resulting in hypochromic and microcytic red cells, ineffective erythropoiesis, hemolysis and a variable degree of anemia **(Kosaryan and Aliasgharian , 2015)**

Beta-thalassemia

β-thalassemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the β chains of haemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals **(Sheth, 2014).**
There are three types of β-thalassemia: (i) β-Thalassemia minor (ii) β-Thalassemia intermediate and (iii) β-Thalassemia major **(Hoffbrandetal., 2012)**
Pathophsiology

The reduced amount (beta+) or absence (beta0) of beta globin chains result in a relative excess of unbound alpha globin chains that precipitate in erythroid precursors in the bone marrow leading to their premature death and hence to ineffective erythropoiesis. The degree of globin chain reduction is determined by the nature of the mutation at the beta globin gene located on chromosome **(sandhyaetal., 2013)**

Deferasirox film coated tablet (Jadenu)
Jadenu (deferasirox) tablets are an oral iron chelation therapy that treats chronic iron overload due to blood transfusions and chronic iron overload in non-transfusion-dependent thalassemia syndromes (NTDT). Jadenu contains the same active ingredient as Exjade® (deferasirox) tablets for oral suspension. Chronic iron overload develops when the body's limited iron storage capacities are exceeded. Since there is no natural mechanism to remove excess iron from the body, iron builds up – first in the liver, and eventually in the heart **(Shander etal.,2009)**

Mechanism of action:

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Jadenu is administered as once-daily oral tablets. It works by attaching to iron which may be stored in different parts of the body, such as the liver and heart, and removes it through the stool. The Jadenu iron complex leaves the body through the digestive system. Removing iron from the body in this way is called chelation. Chelation happens gradually and Jadenu removes a small amount of iron every day, causing iron levels to decrease over time**(Chalmers and Shammo, 2016).**

Pharmacokinetics:-

Absorption

The absolute bioavailability [as measured by area under the curve over time to infinity (AUCinf)] of deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability (as measured by AUCinf) of JADENU tablets was 36% greater than with deferasirox tablets for oral suspension **(Fortin etal., 2018)**

After strength-adjustment, the mean AUCinf of JADENU tablets (i.e., 360 mg strength) was similar to that of deferasirox tablets for oral suspension (i.e., 500 mg strength) under fasting conditions; however the mean Cmax was increased by 30%. The 30% increase in Cmax observed with jadenu tablets is not clinically meaningful. The administration of JADENU tablets with a light meal (approximately 250 calories with fat content less than 7% of total calories) indicated that the AUCinf and Cmax were similar to that under fasting conditions. The administration of JADENU tablets with a high-fat meal (approximately 1000 calories with fat content greater than 50% of total calories), increased AUCinf by 18% and Cmax by 29% compared to that under fasting conditions.

(Fortin etal., 2018)

Distribution

FCT of deferasirox is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of deferasirox FCT confined to the blood cells was 5% in humans. The volume of distribution at steady state (Vss) ofdeferasirox FCT is14.37 ± 2.69 L in adults

Metabolism

Glucuronidation is the main metabolic pathway for deferasirox FCT, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox FCT is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalyzed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). Deconjugation of glucuronide metabolites in the intestine and subsequent reabsorption (enterohepatic recycling) was confirmed in a healthy subjects study in which the administration of cholestyramine 12 g twice daily (strongly binds to deferasirox FCT and its conjugates) 4 and 10 hours after a single dose of deferasirox resulted in a 45% decrease in deferasirox FCT exposure (AUCinf) by interfering with the enterohepatic recycling of deferasirox FCT**(Gao etal., 2011)**

Excretion

Deferasirox FCT and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of deferasirox FCT and metabolites is minimal (8% of the dose). The mean elimination half-life (t1/2) ranged from 8 to 16 hours following oral administration.

Pharmacokinetics in Specific Populations

Pediatric: Following oral administration of single or multiple doses, systemic exposure of adolescents and children to deferasirox FCT was less than in adult patients. In children less than 6 years of age, systemic exposure was about 50% lower than in adults.

Sex: The apparent clearance is 17.5% lower in females compared to males.

Renal Impairment: Compared to patients with MDS and CLcr greater than 60 mL/min, patients with MDS and CLcr 40 to 60 mL/min (n=34) had approximately 50% higher mean deferasirox FCT trough plasma concentrations. **(Huang etal., 2015).**

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Hepatic Impairment: In a single dose (20 mg/kg) study in patients with varying degrees of hepatic impairment, deferasirox FCT exposure was increased compared to patients with normal hepatic function. The average total (free and bound) AUCinf of deferasirox FCT increased 16% in 6 patients with mild (Child-Pugh A) hepatic impairment, and 76% in 6 patients with moderate (Child-Pugh B) hepatic impairment compared to 6 patients with normal hepatic function. The impact of severe (Child-Pugh C) hepatic impairment was assessed in only 1 patient**(Fortin etal., 2018)**

Dosage and administration of Jadenu

Jadenu is a once-daily oral tablet that can be swallowed whole, with water or other liquid, and does not require dispersion in liquid like Exjade, offering a single-step treatment option. This means it can be taken without time-consuming preparation. Jadenu can also be taken with or without a light meal, while Exjade must be taken on an empty stomach. The dosagestrengths of Exjade and Jadenu also differ. **(Huang etal., 2015).**

The original formulation used in Exjade requires the patient to mix and drink the medication in a large glass of water or juice on an empty stomach. Jadenu contains the same active ingredient as Exjade in a formulation that can be taken in a single step and may be taken with a light meal, simplifying administration for patients and providing effective reduction of iron overload **(Chalmers and Shammo, 2016).**

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