Impact of CYP2D6 Polymorphisms on Propranolol Response in Children with Portal Hypertension

Thesis

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List of Abbreviations

Abb.	Full term
ALT	*Alanine transaminase,*
AST	*Aspartate aminotransferase,*
CBC	*Complete blood picture*
CHF	*Congenital hepatic fibrosis*
EM	*Extensive metabolizerCYP2D6: cytochrome P450 2D6*
Fl	*Femtoliters*
GGT	*Gamma glutamyl transferase.*
HR	*Heart rate*
HRV	*Heart rate variability*
HVPG	*Hepatic Venous Pressure Gradient*
INR	*International Normalized Ratio*
LSM	*Liver-stiffness measurement*
MCH	*Mean corpuscular hemoglobin,*
MCV	*Mean corpuscular volume,*
PHG	*Portal hypertensive gastropathy*
PM	*Poor metabolizer*
PV	*Portal vein*
PVT	*Portal vein thrombosis*
TLC	*Total leukocyte count,*
US	*Ultrasound*

INTRODUCTION

Portal hypertension is defined by elevation of hepatic venous pressure gradient (HVPG) greater than 5 mm Hg and it is considered to be clinically significant when HVPG exceeds 10 to 12 mm Hg ***(Fernandez, 2019).***

It is classified based on anatomical location as prehepatic, intrahepatic, or post hepatic portal hypertension. Patients usually present with splenomegaly, life threatening gastrointestinal bleeding and ascites ***(Simonetto et al., 2019).***

The goals of pharmacotherapy treatment of portal hypertension are to reduce mortality and morbidity and prevent complications associated with acute bleeding related to portal hypertension. Two main categories of drugs, vasoconstrictors and vasodilators, are used. The vasoconstrictors are used to treat acute bleeding in patients with portal hypertension before performing endoscopy ***(Garcia-Tsao et al., 2003)***. Vasodilators such as isosorbide mononitrate (ISMN) reduce intrahepatic vascular resistance without decreasing peripheral or portal-collateral resistance **.** Beta-blockers are used to provide primary and secondary prophylaxis ***(Steenen et al., 2016).***

Propranolol is a synthetic non-selective beta-adrenergic receptor blocking agent used in primary and secondary prevention of variceal bleeding in both patients with cirrhosis and non cirrhotic portal hypertension ***(Suk et al., 2007).***

The reduction of heart rate (HR) is still most widely used to direct the administration of propranolol and predict the hemodynamic response ***(Zhang et al., 2016).***

Propranolol acts on the autonomic nervous system and HRV can be used to explore its influence on sympathetic and parasympathetic activity ***(Ernst, 2017).***

CYP2D6 is the rate-limiting enzyme for the metabolism of propranolol and it is involved in its phase I metabolism. CYP2D6 is highly polymorphic and its polymorphisms are based on extent of drug metabolism which includes 4 classes of phenotype ***(Ingelman-Sundberg et al., 1999).***

Factors that influence cytochromes P450 expression and function include genetic polymorphism, epigenetic influences on drug metabolism and non-genetic host factors ***(Zanger and Schwab, 2013).***

AIM OF THE STUDY

Primary goal: To study CYP2D6 polymorphism in Egyptian children with presinusoidal portal hypertension and the correlation of this polymorphism with the effects of propranolol.

Secondary goal: To study the correlation between effective propranolol dose and etiology of portal hypertension.

Chapter 1

PORTAL HYPERTENSION

Definition

Portal hypertension (PHT) indicates increased pressure in portal venous system. Hepatic Venous Pressure Gradient (HVPG) is the difference between the wedged hepatic venous pressure and free hepatic venous pressure. A normal HVPG is 3-5 mmHg. An HVPG above 5 mmHg defines portal hypertension, however an HVPG of 10 mmHg or greater defines clinically significant portal hypertension ***(Fernandez, 2019; Ripoll et al., 2009).***

Etiology of PHT

The causes for portal hypertension are classified as ***(Simonetto et al., 2019).***

I- Prehepatic portal hypertension

1- Portal Vein Thrombosis

2- Splenic Vein Thrombosis

II- Intrahepatic portal hypertension

III- Post-hepatic portal hypertension

I- *Prehepatic portal hypertension*

Prehepatic portal hypertension is an infrequent condition in which increased portal pressure is caused by obstruction of the portal venous tree before it enters the liver. The site of obstruction may be limited to the splenic or mesenteric veins, but most commonly the portal vein is involved ***(Fernandez, 2019)***.

1-Portal Vein Thrombosis

Definition of portal vein thrombosis (PVT): Total or near-total obstruction of blood flow ***(Harmanci and Bayraktar, 2007).***

Etiology of PVT

PVT is the most frequent cause of prehepatic portal hypertension. PVT has various causes. In previous studies, PVT were attributed mostly to trauma (5%-17%), intraabdominal sepsis (5%-36%), umbilical sepsis (5%-12%), pancreatitis (4%-5%) and prothrombotic disorders (2%-28%), but in nearly 50% of the patients etiology remained unidentified ***(Intagliata et al., 2019; Cardin et al., 1992).***

In children, a history consistent with omphalitis or umbilical catheterization can be often obtained. In adults, the cause of portal thrombosis is less frequently identified.

Other risk factors for PVT include factor II mutation, protein C, protein S deficiency and antithrombin deficiency ***(Trebicka and Strassburg, 2014).***

Complications of PVT

The majority of complications of long-standing PVT are due to portal hypertension ***(Intagliata et al., 2019).*** Collateralization of the portal vein might lead to the development of the so-called portal cavernoma ***(Ogren et al., 2006).*** However, portosystemic shunting can also develop, since these cavernous collaterals may not sufficiently drain the portal blood flow, and portal pressure is not sufficiently decreased. This usually presents as de novo appearance and/or progression of gastric or esophageal varices and may be complicated by bleeding ***(Yerdel et al., 2000).*** Bleeding due to PVT occurs about 100 times more often in patients with cirrhosis ***(Intagliata et al., 2019).***

Another but less frequent complication of collateral vessel formation is the portosystemic shunting in some patients, which leads to subclinical hepatic encephalopathy ***(Ogren et al., 2006).***

2- Splenic Vein Thrombosis

Splenic vein thrombosis may be either symptomatic or asymptomatic. Gastrointestinal bleeding at varying severity is the most common manifestation of this syndrome. The main