Centro Hospitalar Trás-os-Montes e Alto Douro

RESEARCH PROTOCOL

The impact of carvedilol posology on Clinically Significant Portal Hypertension: Insights from Elastography Measurements

31 May 2023

Title: The impact of carvedilol posology on Clinically Significant Portal Hypertension: Insights from Elastography Measurements

Name: Bruno Daniel dos Santos Besteiro
Phone Number: +351919818533
E-mail: u014986@chsj.min-saude.pt

Authors: Bruno Besteiro[1,2], Manuel Marques da Cruz[3,4], Cláudia Alves[5], Fátima Costa[6], Mariana Nunes[7], Ana Barreira[8], Joana Calvão[8], Mónica Mesquita[8], Sónia Carvalho[8], Inês Pinho[8] Paulo Carrola[8], José Presa Ramos[8]

Authors Affiliation

1- Internal Medicine Department, Centro Hospitalar e Universitário de São João - Oporto (Portugal)
2- Faculty of Medicine, Oporto University, Centro Hospitalar e Universitário de São João, Oporto, Portugal
3- Unidade de Saúde Pública do Agrupamento de Centros de Saúde Marão e Douro Norte, ARS Norte, Vila Real
4- Faculty of Medicine University of Porto, MEDCIDS and CINTESIS, Porto, Portugal
5- Internal Medicine Department, Hospital Distrital de Santarém – Santarém, Portugal
6- Internal Medicine Department, Centro Hospitalar do Tâmega e Sousa – Penafiel, Portugal
7- Internal Medicine Department, Centro Hospitalar de Trás os Montes e Alto Douro Vila Real, Portugal
8- Liver Unit, Internal Medicine Department, Centro Hospitalar de Trás-os-Montes e Alto Douro - Vila Real, Portugal

Unit: Liver Unit, Internal Medicine Department, Centro Hospitalar de Trás-os-Montes e Alto Douro - Vila Real, Portugal

Introduction / Theoretical foundations:

Transitory elastography is a non-invasive diagnostic method that has been used for the diagnosis and follow-up of patients with clinically significant portal hypertension (CSPH). In this context, the use of targeted therapies to reduce complications resulting from this finding plays a crucial role in managing these patients.

Carvedilol is a non-selective beta-blocker currently considered the first-line drug for treating patients with CSPH. Regarding its pharmacokinetic characteristics, its half-life is approximately 7 to 10 hours. However, there is still a debate in dosing regimen, specially regarding dose interval, with a potential lower bioavalability in once daily regimens

Nevertheless, although the dosing frequency may influence portal pressure and cardiac function, the direct impact on the value of splenic and liver elastography is not fully understood, and there are no studies directly comparing and evalutiang this topic. Therefore, focused studies assessing the impacto f once-daily vs twice daily dosing regimens become essential to improving clinical practice.

Objectives: To assess the acute effects of carvedilol posology in patients with clinically significant portal hypertension (CSPH), as a surrogate marker of bioavailability.

Study design: experimental study including patients with CSPH considered responders to carvedilol prescribed twice daily. These patients had their spleen stiffness measurement (SSM) and liver stiffness measurement (LSM) measured through elastography after suspending their second daily carvedilol intake. Results from the SSM were compared with the values measured while under treatment and before being prescribed with carvedilol. Additionally, comparisons for under treatment with carvedilol and 24-hour suspension were stratified according to carvedilol daily dosage, *D'Amico* classification, the Model for End-stage Liver Disease (MELD) scores, Child-Pugh score, and aetiologies for portal hypertension. The same procedure was repeated for the results of LSM.

Target population: **p**atients with CSPH considered responders to carvedilol prescribed twice daily

Inclusion and exclusion criteria:

Inclusion criteria

- Patients with CSPH (defined as a LSM $\geq$ 25 kPa or SSM over 45kPa prior to introduction of carvedilol)

Exclusion criteria

- Non-responders to NSBB (defined as a reduction of their SSM of less than 10%
- Patients under treatment with any NSBB other than carvedilol
- Patients with a dosing regimen other than twice daily
- Patients with contraindications to NSBB use
- Patients who had not been performed a SSM or LSM through TE while under treatment within 3 months prior to the beginning of the study
- Obesity (defined as body mass index (BMI) > 30 m/kg^2)
- Patients with portal venous thrombosis
- Patients who refused to participate in the study

Recruitment and Selection Process of Participants: Patients admitted to the Liver Unit after meeting the inclusion and exclusion criteria, provided that they agree to participate after being adequately informed about the study.

Variables: gender, age, aetiologies for CSPH, D'Amico classification, the Model for End-stage Liver Disease (MELD) scores (both MELD-Na, and MELD 3.0), Child-Pugh score, and carvedilol daily dosage

Potential benefits/risks of the study: To assess if twice a day prescription may be better in keeping bioavailability of carvedilol and the intended effects of the treatment for CSPH throughout the day.

Confidentiality and Anonymity: Throughout the research development and presentation of results, confidentiality and anonymity of the participants are ensured. When transferring clinical data to the database, each participant will be assigned a code number that allows for

the decoding of their identity. The code will only be accessible to the researchers and will be stored separately from the main database. Access to the computer containing the aforementioned information will be restricted, requiring a specific username and password for each investigator.

Dissemination of Results: The intention is to publish the work in a national/international scientific journal

Duration of the research study: This is a study that will take place over a period of 1 month.

Ethical considerations: The present study will be approved by the ethics committees of each center and will follow the guidelines of Good Clinical Practice, the Declaration of Helsinki, and local laws, as well as the Regulation of the European Parliament and of the Council (EU) 2016/679 on the protection of individuals with regard to the processing of personal data, which was enacted on April 27, 2016.

Direct and indirect costs for CHTMAD and other participating centers: None

Funding and insurance: None

References

1. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959-974.

2. Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, Heinisch BB, Trauner M, Kramer L, Peck-Radosavljevic M; Vienna Hepatic Hemodynamic Lab. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut. 2013 Nov;62(11):1634-41.

3. Reiberger T. The Value of Liver and Spleen Stiffness for Evaluation of Portal Hypertension in Compensated Cirrhosis. Hepatol Commun. 2022 May;6(5):950-964.