A multi-compartmental model of the HepQuant SHUNT test quantifies anatomic shunting and stratifies risk for varices: combined results from the HALT-C and SHUNT-V studies

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1. Introduction

In chronic liver disease (CLD), persistent inflammation and fibrosis impair hepatocyte function and increase portal pressure, resulting in portal venous collaterals and portal-systemic shunting. The HepQuant SHUNT test uses stable nonradioactive 24-^{13}C-cholate (13C-CA) intravenously and 2,2,4,4-d4-cholate (d4-CA) orally to simultaneously measure clearances from both portal and systemic circulations.

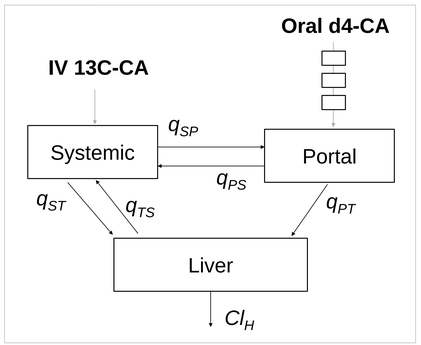
2. Aim

To determine whether compartmental model of the HepQuant SHUNT test could quantify anatomic shunting in CLD patients with esophageal varices.

3. Methods

- A compartmental model was developed using HepQuant SHUNT test results from the HALT-C Trial [1,2], the SHUNT-V Study [3], and lean controls: in total, 492 CLD patients with esophago-gastro-duodenoscopy findings (291 no varices, 143 small varices, 58 large varices) and 26 lean controls.
- A compartmental model (Figure 1) describes dual IV and oral cholate clearance and is divided into 3 compartments: Systemic, Portal, and Liver.
- Transfer between compartments was modeled by a system of 18 differential equations with assumptions from measured and literature-derived values.
- Model parameters were solved for each subject estimated by nonlinear least-squares regression including the anatomic shunt flow (q_{PS}) and portal venous inflow to the liver (q_{PT}).
- Simulations and parameter estimation was solved for each patient on the IV and oral cholate plasma concentration-time data simultaneously.

Figure 1. Compartment Model



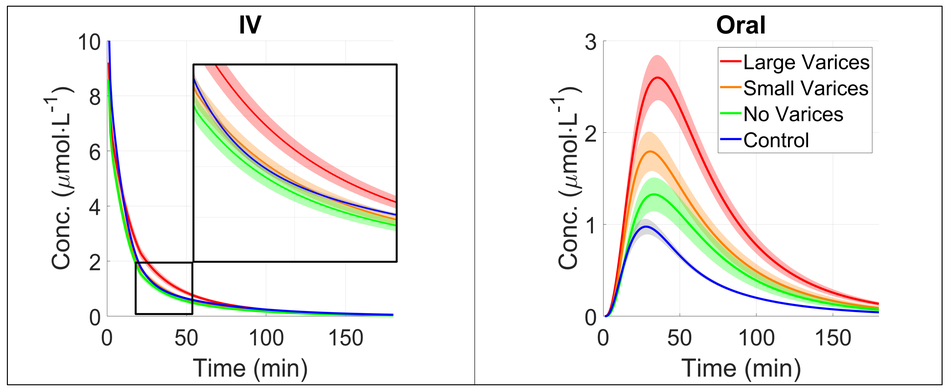
q
flow rates between compartments

Cl_H
total hepatic clearance

4. Results

- The compartmental model fit the data with median adjusted R^2 of 0.99 for the IV 13C-CA curves and 0.95 for the Oral d4-CA curves.
- Significant differences were observed in averaged oral and IV curves between controls, no varices, small varices, and large varices, in plasma concentration-time profiles (Figure 2).
- These results suggest the HepQuant test is detecting the presence and the size/magnitude of anatomic shunts and collateral circulation in patients with varices.

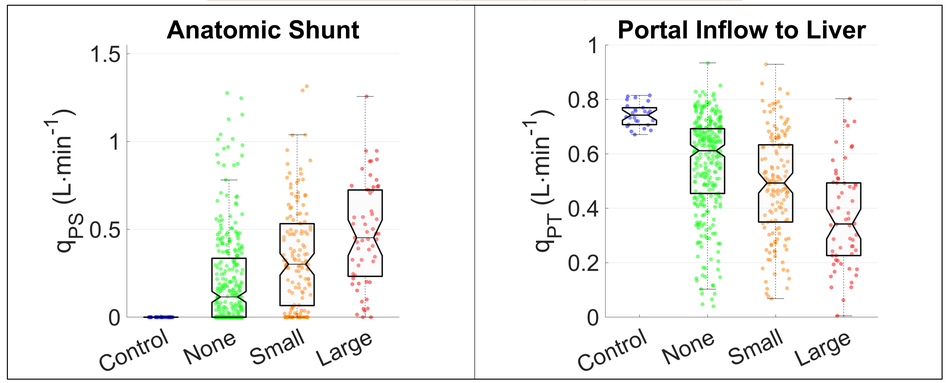
Figure 2. Population-averaged IV curve (left) oral curve (right) simulations (mean and 95% confidence) from the compartment model.



Plasma concentrations normalized to 75 kg bodyweight. Inset on IV curve is magnified view of 20-60 minutes.

- The median anatomic shunt flow rate (q_{PS}) demonstrated significant differences between all groups (Wilcoxon rank-sum $p < 0.05$) (Figure 3, left).
- In parallel, the reduced portal inflow to the liver (q_{PT}) was observed among varices groups, with significant difference between all groups ($p < 0.001$) (Figure 3, right)

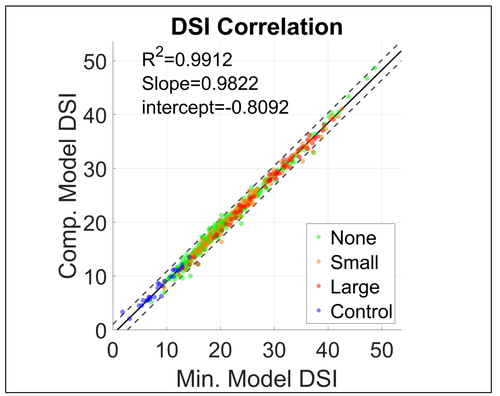
Figure 3. Scatter boxplots of compartmental parameters representing anatomic shunt and portal inflow to the liver across patient groups (control, none, small, and large esophageal varices).



Portal inflow to liver was normalized to 75 kg bodyweight.

Figure 4. Compartmental and Minimal Model DSI Correlation

The disease severity index (DSI) calculated from the compartmental model IV and oral curves correlates well to the DSI calculated from the minimal model IV and oral curves, which was previously validated as a measure of global liver function [4] (Figure 4).



5. Conclusions

- The compartmental model discriminated patients with small and large varices, attributed cholate clearance to hepatocyte function and anatomic shunting, and correlated with validated indices of hepatic disease.
- Compartmental analysis has significant potential to enhance diagnostic performance and clinical utility of HepQuant's global liver function tests.

6. References

[1] Lee, W.M., et al., Evolution of the HALT-C Trial: pegylated interferon as maintenance therapy for chronic hepatitis C in previous interferon nonresponders. Controlled Clinical Trials, 2004. 25(5): p. 472-492.

[2] Everson, G.T., et al., The spectrum of hepatic functional impairment in compensated chronic hepatitis C: results from the Hepatitis C Anti-viral Long-term Treatment against Cirrhosis Trial1. Alimentary Pharmacology & Therapeutics, 2008. 27(9): p. 798-809.

[3] The SHUNT-V Study for Varices, ClinicalTrials.gov study ID: NCT03583996.

[4] Everson, G.T., et al., Portal-systemic shunting in patients with fibrosis or cirrhosis due to chronic hepatitis C: the minimal model for measuring cholate clearances and shunt. Alimentary Pharmacology & Therapeutics, 2007. 26(3): p. 401-410

7. Disclosures

MPM is a paid consultant for HepQuant LLC. SMH and GTE are employees and equity members of HepQuant LLC. All authors have provisional patents pending. HepQuant tests are not FDA approved and are for investigational use only under FDA guidelines for investigational device exemption (IDE).

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