HEPQUANT SHUNT IS SUPERIOR TO CHILD-PUGH IN DEFINING HEPATIC IMPAIRMENT FOR PHARMACOKINETIC STUDIES: EXPERIENCE WITH AMPRELOXETINE (AN ENCORE PRESENTATION)

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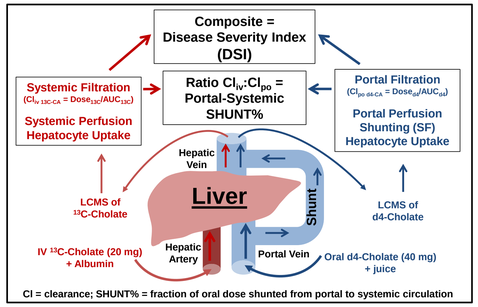
Background and Purpose

- HepQuant SHUNT test quantifies liver function and physiology [1]
- Child-Pugh (CP) classification is the standard classification method for the assessment of hepatic dysfunction in hepatic impairment trials during drug development [2]
- Child-Pugh classification has limitations with respect to stratifying patients with liver disease for quantification of the liver's metabolic capacity and thus is a crude predictor of drug pharmacokinetics [3, 4]
- Ampreloxetine is a novel norepinephrine reuptake inhibitor being developed for treatment of symptomatic neurogenic orthostatic hypotension and is primarily eliminated by the liver
- The aim of this study was to compare the performance of HepQuant with Child-Pugh (CP) classification in predicting the pharmacokinetics of ampreloxetine in subjects with varying degrees of hepatic impairment

HepQuant SHUNT Test Method



HepQuant STAT =
oral d4-cholate concentration at 60 minutes adjusted for 75 kg body weight

STAT is a simple and practical measure that can easily be employed in the clinic

References

1. Burton et al., The within-individual reproducibility of the disease severity index from the HepQuant SHUNT test of liver function and physiology. *Translational Research* (2021) 223: 5-15.
2. Final Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. *Food and Drug Administration*. May 2003 Clinical Pharmacology.
3. El-Khateeb et al., Review article: time to revisit Child-Pugh score as the basis for predicting drug clearance in hepatic impairment. *Alimentary Pharmacology and Therapeutics* (2021) 54: 388-401.
4. Elmeliegy et al., Discordance between Child-Pugh and National Cancer Institute Classifications for Hepatic Dysfunction: Implications on Dosing Recommendations for Oncology Compounds. *Journal of Clinical Pharmacology* (2021) 61(1): 105 - 115

Methods

Clinical Study Design
This was a multicenter, non-randomized, open label, parallel-group, single-dose study (NCT04200573) conducted in adult subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C) and in matching healthy subjects. The study was conducted in two sequential parts with subjects with mild (n = 8) and moderate (n = 7) hepatic impairment enrolled first with corresponding healthy matched controls (n = 7). An additional cohort of subjects with severe (n = 6) hepatic impairment were subsequently enrolled with corresponding healthy matched controls (n = 3 additional). A single ampreloxetine dose of 10 mg was administered to all subjects.

HepQuant SHUNT Test
HepQuant SHUNT test was administered on the day prior to ampreloxetine dosing to establish baseline hepatic function. HepQuant Disease Severity Index (DSI, score of 0 - 50) and SHUNT% (portal-systemic shunting, 0 - 100%) were measured from 5 serum samples obtained within 90 minutes after administration of [24-13C]-cholate intravenously and [2,2,4,4-2H]-cholate orally. Cholate serum concentrations were assessed by LC-MS/MS. Cholate clearances, DSI, and SHUNT% were calculated from the serum cholate concentrations.

Ampreloxetine Pharmacokinetics
PK blood samples were collected at the following times: predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 24, 36, 48, 72, 96, 120, 144, 192, 240, 288, and 336 hr. postdose. Ampreloxetine plasma concentrations were determined by LC-MS/MS. Ampreloxetine PK parameters (C_{max}, $AUC_{0\text{-}inf}$ $t_{1/2}$) were estimated by noncompartmental methods.

Univariate and Multivariate Regression
The software package, MedCalc v20.115, was used for the uni- and multi-variable regression analyses.

Results

Table 1: Baseline Hepatic Function

Child-Pugh Classification	DSI	SHUNT%
Healthy Controls [A, B, C*]	17.7 ± 3.0	25.2 ± 5.9
Child-Pugh A	18.9 ± 3.1	27.1 ± 5.3
Child Pugh-B	26.0 ± 6.1	43.4 ± 17.8
Child-Pugh C	34.3 ± 10.7	61.1 ± 22.1

* Matched to Child-Pugh A, B, and C subjects

- DSI and SHUNT% increased with increasing Child-Pugh severity class

Table 2: Ampreloxetine PK Parameters after a Single 10 mg Dose to Healthy Subjects and Subjects with Hepatic Impairment (Child-Pugh A, Child-Pugh B, and Child-Pugh C)

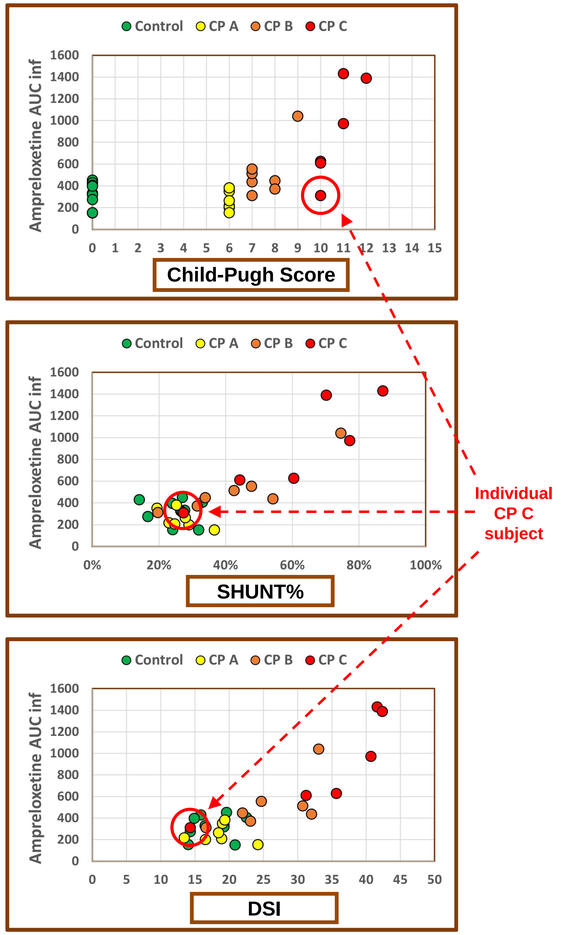
Child-Pugh Classification	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng.hr/mL)	$t_{1/2}$ (hr)
Healthy Controls [A&B*]	5.22 ± 1.00	303 ± 111	48.3 ± 12.1
Healthy Controls [C**]	5.69 ± 1.47	339 ± 113	50.3 ± 14.9
Child-Pugh A	4.68 ± 0.66	253 ± 83.8	47.7 ± 16.7
Child Pugh-B	5.24 ± 1.47	525 ± 242	70.1 ± 20.0
Child-Pugh C	5.66 ± 2.10	890 ± 454	142 ± 85.4

* Matched to Child-Pugh A and B subjects; ** Matched to Child-Pugh C subjects

- $AUC_{0\text{-}inf}$ and half-life increased ~ 1.7-fold and ~ 2.5-fold in subjects with moderate and severe hepatic impairment

Results

Figure 1: Correlations between Child-Pugh Score, SHUNT%, DSI, and Ampreloxetine $AUC_{0\text{-}inf}$



- Similar performance for HepQuant STAT (not shown) as for SHUNT% and DSI

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Results

Table 3: Multivariable Regression Analyses for Predictors of Ampreloxetine $AUC_{0\text{-}inf}$ in Liver Disease

Multivariate Regression	p-values (DSI Model)	p-values (SHUNT% Model)
HepQuant Variable	0.0143 (DSI)	0.0024 (SHUNT%)
Child-Pugh Score	0.31	0.40
Age	0.36	0.73
Gender	0.30	0.16
Ethnicity	0.59	0.49
BMI	0.32	0.95
	Coefficient of Determination, r^2	
HepQuant Variable	0.8519 (DSI)	0.8851 (SHUNT%)

Values for DSI, SHUNT%, Child-Pugh Score, age, gender, ethnicity, and BMI represent p-values for each variable evaluated in multi-variable regression analysis. Coefficient of determination reflects the coefficient for the HepQuant variable that is a significant predictor of ampreloxetine $AUC_{0\text{-}inf}$

- DSI and SHUNT% were the only significant predictors of ampreloxetine $AUC_{0\text{-}inf}$ in multivariate regression models

Conclusions

- Ampreloxetine plasma exposure (AUC0-inf) is increased in subjects with moderate (1.7-fold; Child-Pugh B) and severe (2.5-fold; Child-Pugh C) hepatic impairment
- Ampreloxetine exposure (AUC0-inf) correlates with Child-Pugh score and more strongly with the HepQuant parameters SHUNT% and DSI
  - Similar performance for the simple, practical HepQuant STAT test
- Variability is observed in ampreloxetine exposure (AUC0-inf) in subjects with moderate (CP B) and severe hepatic impairment (CP C). The variability can be explained for individual subjects by their DSI and SHUNT%.
- Multivariable regression models demonstrate DSI and SHUNT% as superior predictors of ampreloxetine exposure (AUC0-inf) relative to Child-Pugh score
- HepQuant DSI and SHUNT% (as opposed to CP class) may be more useful predictors of drug exposure and thus serve to better optimize dose recommendations for novel therapeutics in patients with liver disease.

Disclosures
Jitendra Kanodia, Hugh Giovinazzo, Wayne Yates, and David L. Bourdet are current or former employees of Theravance Biopharma. Steve M. Helmke is a HepQuant employee (CSO) and equity member and has intellectual property in HepQuant technology; Gregory T. Everson is a HepQuant employee (CEO) and equity member and has intellectual property in HepQuant technology.