Incorporating Bile Salt Export Pump (BSEP) Inhibition in The Rule-of-Two (RO2) Model to Predict the Risk of Drug-Induced Liver Injury (DILI)

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Introduction

- Idiosyncratic drug-induced liver injury (DILI) is a major safety concern during drug development and in clinical practice. [1]
- There is an unmet need for a predictive classification method with high sensitivity and specificity for predicting DILI.
- The "Rule of Two" (RO2; daily dose ≥ 100 mg and logP ≥ 3) has been proposed as a framework for predicting DILI;[2] however, the low sensitivity associated with RO2 suggests the need for further refinement.

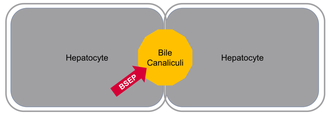


Figure 1: Localization of BSEP in the Hepatocyte

- A proposed mechanism of DILI is inhibition of bile salt export pump (BSEP), the primary transporter that secretes bile acids out of the hepatocytes; however, the utility of *in vitro* BSEP inhibition data as a predictor of DILI is unclear. [3-5]

Objective

- The objective of this research was to evaluate BSEP inhibition as a predictor of DILI and to investigate the utility of combining BSEP inhibition with the RO2 to predict DILI.

Methods

Dataset:

- Drugs classified as either Most-, Less-, or No-DILI in the DILIRank dataset were selected for inclusion in the dataset.

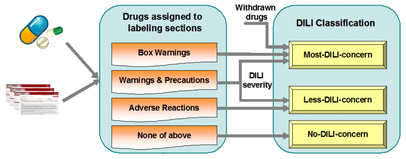


Figure 2: DILI Classification in DILIRank Dataset[6]

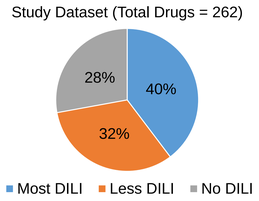
- RO2 classification, BSEP inhibition data and pharmacokinetic data (dose, $C_{max\ (steady\ state)}$, protein binding) were added to the dataset.
- RO2, BSEP, and a combined criteria of RO2 or BSEP inhibition were tested as predictors of DILI. Sensitive, specificity, negative and positive predictive values, and overall accuracy were determined.
- Different definitions of BSEP inhibition were evaluated as described below.

Method 1: IC_{50}	An IC_{50} <100 µM was used to define transporter inhibition
Method 2: $C_{max,ss}/IC_{50}$ ratio	An empiric $C_{max,ss}/IC_{50}$ ratio ≥ 0.1 and a receiver operating characteristic (ROC)-analysis derived $C_{max,ss}/IC_{50}$ ratio were used to define BSEP inhibition

Results

Category	Classification	N	%
RO2	Positive	63	24%
	Negative	199	76%
BSEP	IC_{50} < 100 µM	89	34%
	IC_{50} ≥ 100 µM	173	66%

Table 1: Composition of Study Dataset. Number of drugs meeting the specified criteria in the final study dataset.



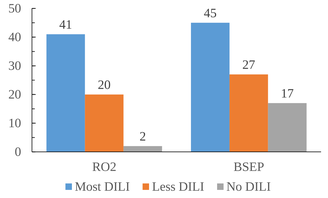


Figure 3: Number of Drugs in Each DILI Category in The Final Study Dataset. (A) Number of drugs classified as Most-, Less-, or No-DILI. (B) Number of drugs meeting the specified criteria in each DILI category. Inhibition of BSEP was defined as IC_{50} < 100uM.

	SN(%); SP (%)	PPV(%); NPV(%)	Accuracy (%)	MCC	Odds Ratio (p-value)
RO2	39; 97	95; 53	63	0.42	23.1 (<0.0001)
BSEP (IC_{50} <100 µM)	43; 77	73; 49	57	0.21	2.5 (0.0068)
RO2, BSEP*	56; 75	76; 54	64	0.31	3.85 (<0.0001)

Table 2: Predictive Performance of Each Criterion Comparing Drugs in The Most and No DILI Categories. Inhibition of BSEP was defined as IC_{50} < 100uM, N=177. SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; MCC, Matthew's Correlation Coefficient.

Acknowledgements

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References

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3. Dawson S, et al. *Drug Metab Dispos.* 2012
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Results

	SN; SP	PPV; NPV	Accuracy	MCC	Odds Ratio (p-value)
RO2	65; 96	97; 55	74	0.56	42.4 (0.0004)
C_{max} ≥ 1 µM	65; 79	88; 50	69	0.41	7 (0.0008)
	Empiric: Total $C_{max,ss}/IC_{50}$ ratio ≥ 0.1				
BSEP ($C_{max,ss}/IC_{50}$)	43;88	88;40	56	0.29	5.194 (0.0148)
RO2, BSEP# ($C_{max,ss}/IC_{50}$)	76;88	93;62	79	0.59	22.076 (<0.0001)
	ROC-Derived: Total $C_{max,ss}/IC_{50}$ ratio ≥ 0.0382				
BSEP ($C_{max,ss}/IC_{50}$)	74; 83	91; 59	77	0.53	14.3 (<0.0001)
RO2, BSEP ($C_{max,ss}/IC_{50}$)	89; 83	92; 77	87	0.71	40 (<0.0001)

Table 3: Predictive Performance of Each Criterion Comparing Drugs in the Most- and No-DILI Categories. Inhibition of BSEP was defined using Cmax,ss/IC_{50} ratio. N=78. SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; MCC, Matthew's Correlation Coefficient.

Conclusions

- Although RO2 and BSEP inhibition have previously been reported to be predictive of DILI, drugs that are positive for these criteria are limited.
- RO2 positive compounds and BSEP inhibitors were more common in Most- or Less-DILI categories compared to No-DILI.
- $C_{max,ss}/IC_{50}$ ratios were better inhibition thresholds for BSEP compared to IC_{50} alone.
- Incorporating both RO2 and $C_{max,ss}/IC_{50}$ based BSEP inhibition resulted in improved predictions for DILI.
- A sequential approach of assessing the RO2 criteria followed by evaluating for BSEP inhibition improves the likelihood of predicting the potential for a compound to show DILI.