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Liver Safety Comparison of Two Treatments for Autosomal-Dominant Polycystic Kidney Disease (ADPKD) Using Quantitative Systems Toxicology Software (DILIsym)

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PURPOSE

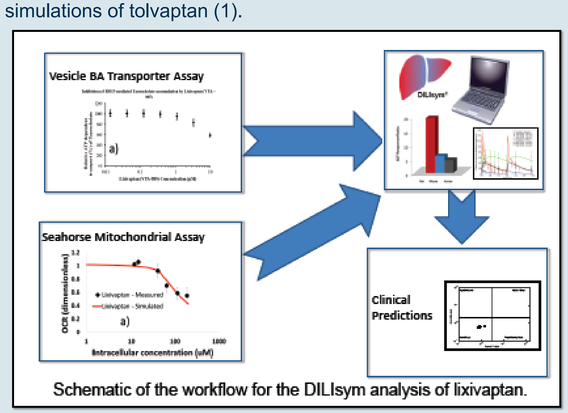
Lixivaptan, a vasopressin-2 receptor antagonist, is being developed for the treatment of autosomal-dominant polycystic kidney disease (ADPKD), an orphan disease that is an unmet medical need. We prospectively compared the potential for lixivaptan to cause liver toxicity to another drug in the same class, tolvaptan, which has produced off-target liver signals in clinical trials (1).

OBJECTIVE

The main objective of this research was to determine if a next-in-class compound would provide a better liver safety profile than the first-in-class comparator for treatment of an important unmet medical need, ADPKD.

METHOD

In vitro data relating to reactive oxygen species formation, mitochondrial toxicity, and bile acid transporter inhibition for lixivaptan and its metabolites were collected. Using these data, lixivaptan and its metabolites were represented in DILIsym, QST software for predicting drug-induced liver injury. Lixivaptan PBPK was also represented within DILIsym, incorporating clinical trial PK data. Proposed ADPKD treatment dosing regimens were simulated and compared to previously published DILIsym simulations of tolvaptan (1).

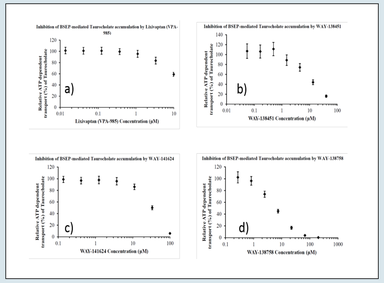


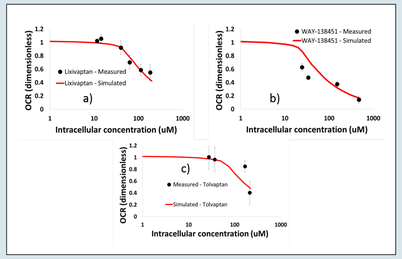
Schematic of the workflow for the DILIsym analysis of lixivaptan.

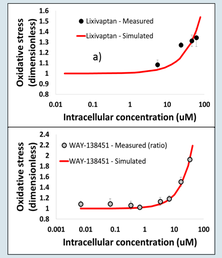
RESULTS

In Vitro Results

In vitro experiments measured mitochondrial dysfunction, ROS generation, and bile acid transporter inhibition due to all four chemical species. For the mitochondrial assay and the ROS assay, a parallel culture was run in order to assess the intracellular concentration present in each assay; the assay results were corrected for these concentrations before the parameter values were calculated.

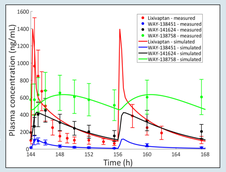


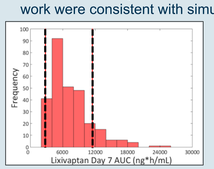




PBPK Representation

The PBPK representation for lixivaptan and its major metabolites was constructed using clinical data for optimization and validation. The clinical trials used were Phase I trial results (n = 67) for seven-day 100 mg BID and 400 mg BID dosing regimens. The simulation results reasonably matched the data. Liver accumulation data from a rat WBAR study and from *in vitro* studies collected for this work were consistent with simulated liver concentrations.



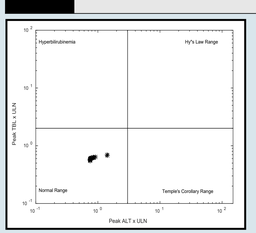


The exposure range of the customized SimPops was validated against the observed exposure range from the clinical trial data for all four chemical species (lixivaptan is shown at left). The range of simulated exposures aligned well with the observed data; outliers were expected based on the fact that the simulated population was larger than the population in the clinical trial.

DILIsym Simulation Results

Simulations predicted lixivaptan to be less toxic than tolvaptan; while tolvaptan had significant ALT elevations in its SimPops simulation, lixivaptan had only sub-clinical ALT elevations. Simulations for lixivaptan suggested a low rate of ALT elevations at 400 mg BID, which suggests that the simulation results may be slightly conservative. ROS was found to be the main mechanism responsible for simulated ALT elevations at the supratherapeutic dose, in contrast with the case of tolvaptan in which bile acid accumulation and ETC inhibition were found to be the mechanisms of toxicity (1).

Drug	Dose and Duration	Parameter Settings	Clinical ALT > 3X ULN	Simulated ALT > 3X ULN
Lixivaptan	200/100 mg QD, 12 wks	Default measured	Study not yet conducted	0/285
Tolvaptan (1)	90/30 mg QD, 24 wks	Default measured	4.4%	18/229 (7.86%)



DILIsym Parameter Input Comparison

Mechanism	DILIsym Parameter	Unit	Value****				
			Lixivaptan	WAY-138451	WAY-141624	WAY-138758	Tolvaptan**
Mitochondrial Dysfunction	Coefficient for ETC inhibition	µM	535	250	N/A	N/A	729
Oxidative Stress	RNS/ROS production rate constant	mL/nmol/hr	5.45×10^{-4}	2.12×10^{-3}	N/A	N/A	N/A
Bile Acid Transporter Inhibition	BSEP inhibition constant	µM	15*	8.6*	39.5*	5.6*	10***
	NTCP inhibition constant	µM	19*	N/A	85.8*	8.9*	N/A
	Basolateral inhibition constant**	µM	70*	54*	16.3*	4*	N/A

* Values are IC_{50} values; mode of inhibition was not measured *in vitro*. In a sensitivity analysis, the worst-case inhibition scenario (noncompetitive BSEP and basolateral inhibition, competitive NTCP inhibition) was assumed; toxicity results were unaffected. As a result, mode of inhibition was determined to not affect the simulation and K_i investigation studies were not commissioned.

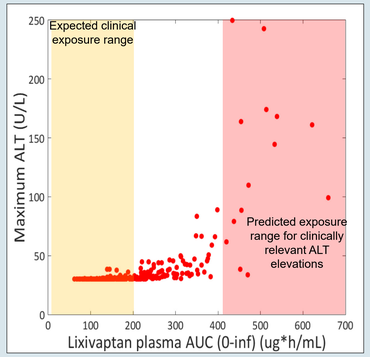
** Tolvaptan parameters are taken from *in vitro* experiments undertaken for this research. Previously published DILIsym parameters are available in Woodhead et al., Tox. Sci. 2017 (1). The published ETC inhibition parameter was 1030 µM, which is not significantly different from the measured value here.

*** IC_{50} value for tolvaptan was measured for this research. A K_i value was measured for the previously published tolvaptan work; the published value is somewhat higher than the value reported here. However, personal communication with the experimentalists suggested that the initial IC_{50} value calculated in that experiment was not substantially different from that measured here.

**** Comparisons of parameter values should be undertaken with caution, as they must be placed in context with exposure for their full usefulness.

RESULTS

Exposure-Toxicity Relationship



The simulation of lixivaptan at the supratherapeutic dose of 400 mg BID shows a distinct relationship between exposure and ALT elevations. From this relationship, it is apparent that the expected exposure range for the 200/100 mg split daily dose proposed for use in the clinic is well below that which produces clinically significant (>3X ULN) ALT elevations in the simulations. This also stands in contrast with tolvaptan, where no exposure-response relationship was observed in the clinic (2) and where simulations suggest that exposure-related parameters are not risk factors for toxicity (1).

CONCLUSIONS

Lixivaptan was predicted to be safer than tolvaptan with respect to the liver toxicity mechanisms represented in DILIsym. Quantitative and qualitative differences were identified between the two drugs. These findings paved the way for confirmatory clinical trials with lixivaptan in ADPKD. ***Palladio Biosciences was granted IND clearance for its Phase II study with lixivaptan in April of 2018. The study is ongoing.***

ACKNOWLEDGEMENTS

- Palladio Biosciences, Inc.
- The members of the DILI-sim Initiative

(1) Woodhead et al., Toxicol Sci.; 2017. (2) Watkins et al., Drug Safety, 2015.

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