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

Woodhead, J.L.*, Pellegrini, L.#, Siler, S.Q. *, Shoda, L.K.M. *, Watkins, P.B. *, Howell, B.A. *

*DILIsym Services, Inc., a Simulations Plus Company, Research Triangle Park, NC, USA; #Palladio Biosciences, Inc., Newtown, PA

ABSTRACT

Objectives: Lixivaptan, a vasopressin-2 receptor antagonist, is in development for the treatment of ADPKD, an orphan disease with high unmet medical need. The main objective of this research was to prospectively compare the potential for lixivaptan to cause liver toxicity to a comparator drug in the same class, tolvaptan, which has produced off-target liver signals in clinical trials[1].

Methods: *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, a platform QST model of drug-induced liver injury. Lixivaptan PBPK was also represented within DILIsym, incorporating clinical trial PK data. Proposed ADPKD treatment dosing regimens were simulated and the predicted potential for liver enzyme elevations was compared to that previously determined for tolvaptan in DILIsym[2].

Results: Lixivaptan was not predicted to cause liver enzyme elevations in a simulated human population which includes variability in toxicity susceptibility and pharmacokinetics, while tolvaptan was correctly predicted to cause rare liver enzyme elevations in a similar population (Table 1). Mechanistic simulations at supratherapeutic doses suggest that potential liver toxicity mechanisms for lixivaptan are different from those identified for tolvaptan.

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 pave the way for confirmatory clinical trials with lixivaptan in ADPKD.

INTRODUCTION

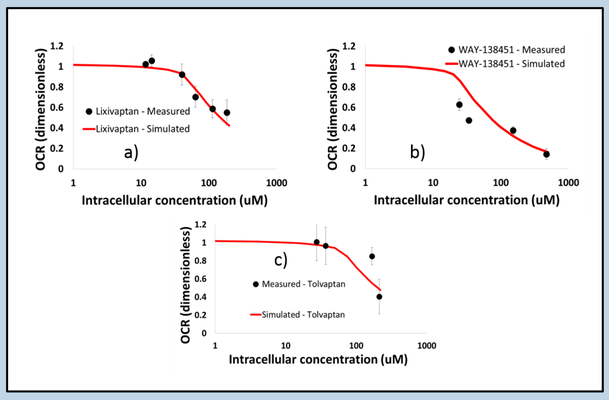
- Lixivaptan is a V2 vasopressin receptor antagonist that is under investigation for the treatment of autosomal-dominant polycystic kidney disease (ADPKD), an inherited orphan disease characterized by progressive kidney failure.
- Lixivaptan is in the same class of drugs as tolvaptan, an investigational ADPKD treatment that caused liver toxicity in a Phase III clinical trial.
- In previous work, DILIsym was employed to model tolvaptan-mediated liver injury; DILIsym was able to recapitulate the observed toxicity, implicating a combination of bile acid transporter inhibition and mitochondrial electron transport chain (ETC) inhibition as responsible for the toxicity.
- A DILIsym representation was thus constructed for lixivaptan and its three major metabolites, WAY-138451, WAY-141624, and WAY-138758, in order to compare the potential for lixivaptan to cause hepatotoxicity with that simulated for tolvaptan.

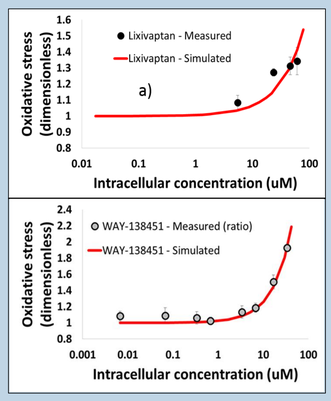
METHODS

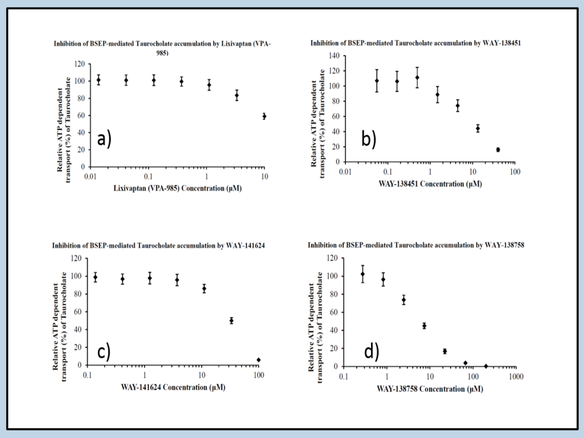
- *In vitro* toxicity data were collected in order to determine the effect of lixivaptan and its three major metabolites on oxidative stress generation, bile acid transporter inhibition, and mitochondrial dysfunction. Lixivaptan and WAY-138451 had an effect on all three mechanisms; WAY-141624 and WAY-138758 were bile acid transporter inhibitors but did not induce oxidative stress or affect the mitochondria.
- DILIsym parameter values were calculated using the *in vitro* data for each of the mechanisms for which an effect was measured. Calculated IC_{50} values were used as K_i values for inputs; mitochondrial dysfunction was modeled in MITOsym, and oxidative stress was modeled in DILIsym.
- A PBPK representation for lixivaptan and its metabolites was constructed within DILIsym using plasma time course data for all four chemical species as well as *in vitro* and *in vivo* liver accumulation data.
- A customized SimPops was created to charaterize lixivaptan exposure variability. This SimPops was based on the v4A_1 SimPops included in DILIsym v6A which includes variability in parameters related to each of the toxicity mechanisms represented in DILIsym. A SimPops with variability in exposure-related parameters was created and superimposed upon the v4A_1 SimPops.
- Clinical trial protocols and proposed protocols for lixivaptan were simulated and compared to published simulation results for tolvaptan.

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.

Calculated Parameter 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

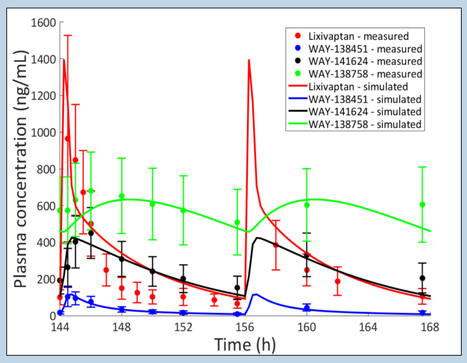
* Values are IC_{50} values; mode of inhibition was not measured *in vitro*. In a sensitivity analysis, the worst-case inhibition scenario (noncompetitive BSEP and basolateral inhibition, competitive NTCP inhibition) was assumed; toxicity results were unaffected. As a result, mode of inhibition was determined 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. 2016[2]. 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.

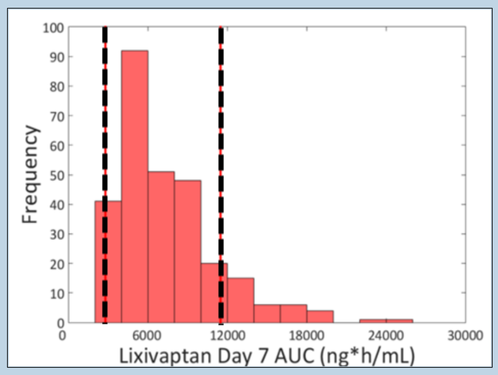
**** Comparisons of parameter values should be undertaken with caution, as they must be placed in context with exposure for their full usefulness.

PBPK Representation and Custom SimPops



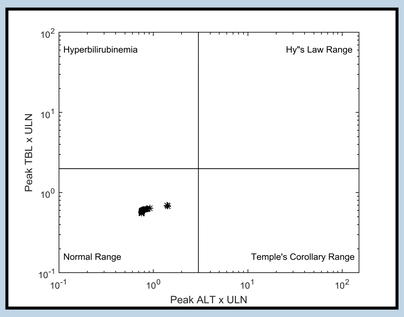
The PBPK representation for lixivaptan and its major metabolites was constructed using clinical data for optimization and validation. The clinical trials used were Phase I trial results (n = 67) for seven-day 100 mg BID and 400 mg BID dosing regimens. The simulation results reasonably matched the data. 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 right). 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.



Simulation Results

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^	90/30 mg QD, 24 wks	Default measured#	4.4%	18/229 (7.86%)



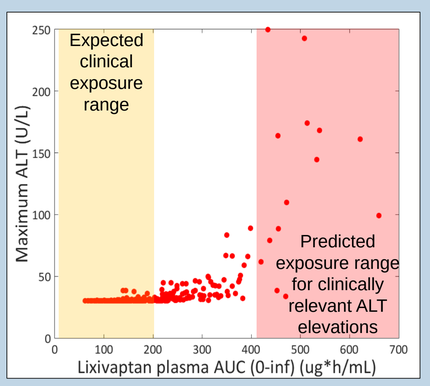
Dose and Duration	Parameter Settings	Clinical ALT > 3X ULN	Simulated ALT > 3X ULN
100 mg BID for 60 days	Default measured	On treatment similar to placebo	0/285
200 / 100 mg for 12 weeks	Default measured	Clinical study not yet conducted	0/285
400 mg BID for 7 days	Default measured	0/67	7/285

Dose and Duration	Parameter Settings	Simulated ALT > 3X ULN
400 mg BID, 7 days	Default measured	7/285
400 mg BID, 7 days	No parent-generated ROS	0/285

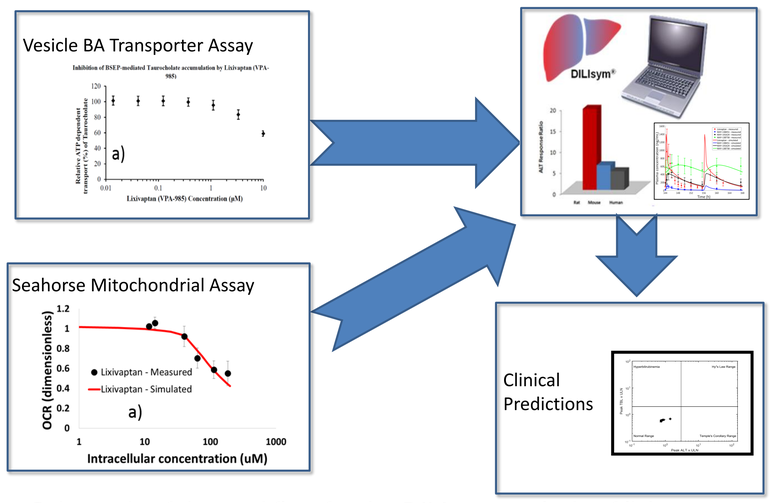
Simulations predicted lixivaptan to be less toxic than tolvaptan; while tolvaptan had significant ALT elevations in its SimPops simulation, lixivaptan had only sub-clinical ALT elevations. Simulations for lixivaptan suggested a low rate of ALT elevations at 400 mg BID, which suggests that the simulation 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[2].

^ Tolvaptan simulation results are from Woodhead 2016[2].

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[1] and where simulations suggest that exposure-related parameters are not risk factors for toxicity[2].



Schematic of the workflow for the DILIsym analysis of lixivaptan.

CONCLUSION

Simulations predicted lixivaptan to be less likely than tolvaptan to cause liver injury in clinical trials for ADPKD. Furthermore, mechanistic differences between lixivaptan and tolvaptan were identified, suggesting that it would be even more unlikely for lixivaptan to replicate tolvaptan's negative clinical experience. The simulations therefore support the continued development of lixivaptan for ADPKD treatment. This research demonstrates the potential for using QST techniques to prospectively compare molecules in the same class for toxic potential in order to select the molecule that is most likely to succeed.

ACKNOWLEDGEMENTS

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

DILIsym Services — A SIMULATIONS PLUS COMPANY

References available upon request

PALLADIO BIOSCIENCES