In Vitro Drug Interaction Studies of UNI-494 Indicate Low Risk of Drug-Drug Interactions

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BACKGROUND

- Nicorandil, a selective mitochondrial ATP-sensitive potassium channel activator,[1] may be a promising acute kidney injury treatment, but its clinical use is limited by serious gastrointestinal (GI) side effects and rapid absorption and elimination[2,3]
- UNI-494, a novel nicorandil prodrug designed to improve the pharmacologic properties of nicorandil, may increase the short half-life and improve the safety profile of nicorandil
- As drug-drug interactions (DDI) are usually adverse clinical effects, pre-clinical evaluations of DDI risk are an important part of new drug development

OBJECTIVE

We present results from 3 pre-clinical studies of UNI-494, with the goal of evaluating DDI risk

METHODS

- UNI-494 at concentrations of 0.1 and 1 μM were individually added to the plasma of rats, dogs, and humans, and the in vitro plasma protein binding was determined by the ultrafiltration method
- Each concentration was tested in triplicate
- To evaluate transporter inhibition of P-GP, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K, probe substrate transport was measured in the presence and absence of UNI-494
- To evaluate the inhibition of cytochrome P450 enzymes by UNI-494 (<100 μM), automated samples were prepared using a single substrate cocktail incubation with pooled human liver microsomes (0.1 mg/mL), with 0- and 30-minute NADPH pre-incubation and a 5-minute substrate incubation time
- Metabolite formation in the incubation cocktail was analyzed by LC-MS/MS, including deuterated internal standards

RESULTS

- The in vitro plasma protein binding ratios of UNI-494 at concentrations of 0.1 μM and 1 μM were 84.3% and 84.9% in rats; 83.1% and 85.3% in dogs; and 83.7% and 82.7% in humans, respectively **(Figure 1)**
- At IC_{50} >100 μM, UNI-494 did not inhibit OATP1B1, OATP1B3, or OAT3 and weakly inhibited BCRP and P-glycoprotein
- At IC_{50} ≤100 μM, UNI-494 showed weak or no inhibition of all CYP450 enzymes tested, with only CYP2D6 approaching moderate inhibition **(Figure 2)**

Figure 1. Mean (±SD) In Vitro Plasma Protein Binding of UNI-494 in Rat, Dog, and Human Plasma

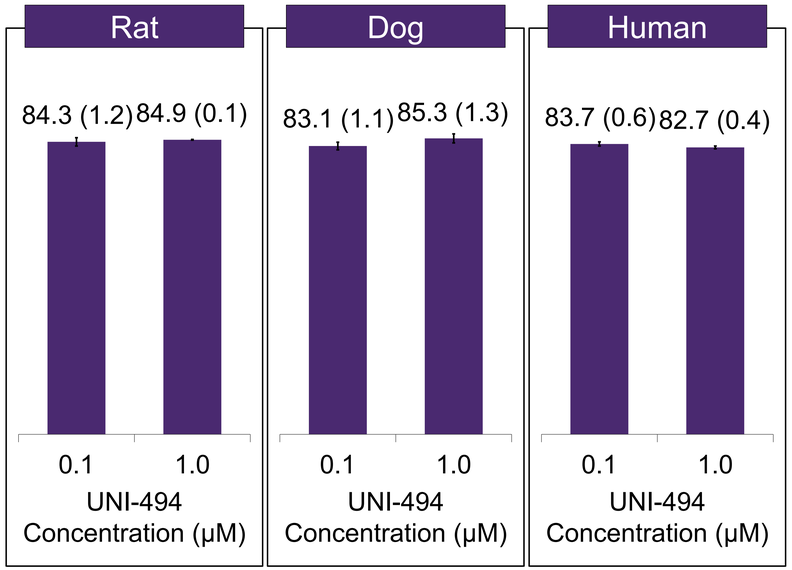

Figure 2. Mean (±SE) IC_{50}[1] of Cytochromes by UNI-494 (≤100 μM)

Enzyme	Substrate Reaction	IC_{50}[1] (μM) 0 Min Incubation	IC_{50}[1] (μM) 30 Min Preincubation + NADPH
CYP2C9	S-mephenytoin 4'-hydroxylation	>100	>100
CYP2C19	Paclitaxel 6α-hydroxylation	>100	>100
CYP2C8	Diclofenac 4'-hydroxylation	>100	72 (7)
CYP1A2	Phenactin O-dealkylation	>100	62 (13)
CYP3A4/5	Midazolam 1'-hydroxylation	>100	19 (4)
CYP2B6	Bupropion hydroxylation	70 (7)	21 (5)
CYP2D6	Dextromethorphan O-demethylation	42 (15)	11 (3)

1 Amount of UNI-494 needed to inhibit an enzyme by 50%

CONCLUSION

- These results indicate that plasma protein binding for UNI-494 is high and it is not concentration dependent
- UNI-494 had little to no inhibition of the hepatic transporters or CYP enzymes tested

IMPLICATIONS

- UNI-494 may have a low risk of DDI
- Future studies in patients are warranted

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