CTP-692: Selective deuterium modification of D-serine markedly decreases renal toxicity in preclinical testing

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Abstract

CTP-692, a deuterated version of the naturally occurring amino acid D-serine, is being developed as an adjunctive treatment for schizophrenia. CTP-692 and D-serine each bind to the glycine modulatory site of the human NMDA receptor (NMDAR) with indistinguishable affinities and produce similar functional activation of the NMDAR in the presence of glutamate. In some human clinical studies, D-serine has demonstrated a benefit on negative and cognitive symptoms of schizophrenia, as well as effects on positive symptoms. However, the use of D-serine as a human therapeutic may be limited by concerns regarding nephrotoxicity observed in rats. CTP-692 provided greater AUC exposure and a longer half-life than corresponding doses of D-serine *in vivo*. Notably important markers of nephrotoxicity, serum creatinine and blood urea nitrogen, were highly elevated with D-serine but were within normal values with CTP-692 in rats. Based on the improved pharmacokinetic and toxicological profiles in rats, CTP-692 may provide an improved therapeutic window compared to D-serine while preserving the intrinsic pharmacology at the NMDAR. Phase 1 clinical testing of CTP-692 is expected to begin by year-end 2018.

Introduction

Deuterium (a non-radioactive isotope of hydrogen) is very similar to hydrogen except that the mass is twice that of hydrogen. Because of the increased mass, deuterium forms a chemical bond with carbon that is stronger than the carbon-hydrogen bond. In some cases, deuterium modification will decrease the rate of metabolism as a result of slower carbon-deuterium bond cleavage resulting in reduced metabolite formation. (Foster, 1985; Shao, 2010). In select cases, the new molecule with deuterium modification has enhanced metabolic properties while preserving the intrinsic pharmacological activity.

There has been significant interest in the use of D-serine for the treatment of schizophrenia but development has been limited because of concerns of nephrotoxicity. Here we describe that selective substitution in D-serine of hydrogen by deuterium (resulting in CTP-692) did not change the compound's ability to co-activate the NMDA receptor, but increased preclinical metabolic stability and remarkably decreased markers of kidney toxicity on acute dosing *in vivo*.

For all experiments described here, D-serine was purchased from Sigma-Aldrich while CTP-692 was supplied by Concert Pharmaceuticals, Inc.

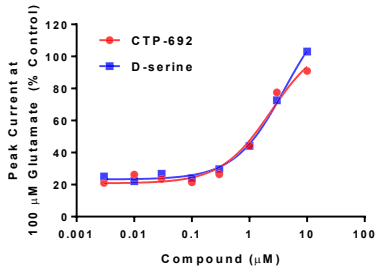
CTP-692 and D-serine have similar intrinsic pharmacology

The binding and activation of receptors by D-serine and CTP-692 were similar in all cases where they were measured. Compared to the non-deuterated compound, CTP-692 demonstrated nearly identical *in vitro* binding affinity for the glycine modulatory site of NMDAR. For the binding affinity of CTP-692 to the glycine site of NMDA receptor from rat cerebral cortical membranes, the average K_i for CTP-692 was 0.91 µM while the average K_i for D-serine was 0.95 µM.

CTP-692 and D-serine have similar activity at the NMDA receptor

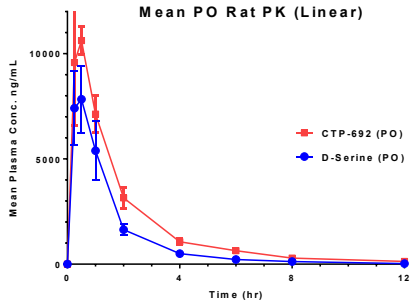
The activation of the NMDA receptors by CTP-692 and D-serine was assessed in an automated patch clamp system (ScreenPatch©) using HEK293 cells expressing human NMDAR subunits GluN1 and GluN2A.

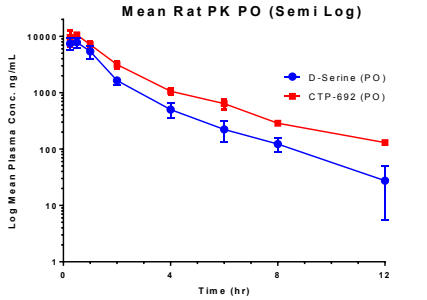
Cells were treated with increasing concentrations of CTP-692 or D-serine (0.003 to 10 µM). Peak current and steady state current were measured. The activity at the NMDA receptor was indistinguishable for the two compounds. A representative graph is depicted.



CTP-692 has a greater $t_{1/2}$, C_{max}, and AUC, and a similar t_{max} and %F as D-Serine when dosed PO in rats

Sprague-Dawley Rats were dosed with CTP-692 or D-serine PO at 10 mg/kg in 0.5% MC and IV in PBS at 5 mg/kg. Plasma levels of CTP-692 and D-serine were evaluated using non-compartmental (NCA) PK. Greater exposure and a longer half-life are achieved with CTP-692 vs D-serine with both IV (not shown) and PO dosing.



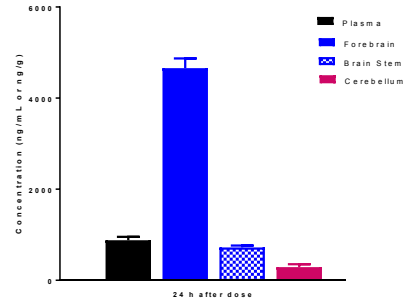


Compound	$t_{½}$ (h)	t_{max} (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng*h/mL)	%F
CTP-692	2.66 (17.7)	0.417 (34.6)	11400 (13.3)	21500 (5.9)	93%
D-serine	1.77 (37.8)	0.417 (34.6)	8780 (14.8)	13200 (14.3)	114%
CTP-692 to D-serine ratio	1.5	1.0	1.3	1.6	N/A

CTP-692 was also dosed IV/PO in dogs and a similarly large %F was observed (~87%).

CTP-692 accumulates in the rat forebrain (site of action)

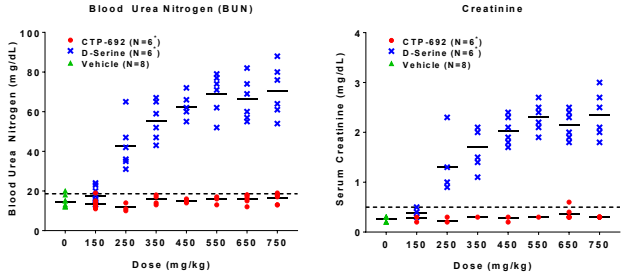
After dosing rats with CTP-692 PO at 100 mg/kg at 24h tissues from perfused brain and plasma were collected and analyzed by LC-MS. The concentration of CTP-692 in the forebrain (location of the target of interest) is greater than plasma or other brain locations.



Normal BUN and creatinine levels observed in rats dosed with CTP-692

Rats were dosed PO with either CTP-692, D-serine or vehicle. Rats were dosed in 100 mg/kg increments from 150 mg/kg to 750 mg/kg with either CTP-692 or D-serine. Serial PK was collected to confirm exposure. Clinical chemistry was performed 24 hours after dosing. In all cases the AUC and C_{max} for each dose group was larger for the rats receiving CTP-692 vs D-serine. The AUC was dose linear for both CTP-692 and D-serine, however the C_{max} was not dose linear above ~400mg/kg. For both compounds, none of the rats showed visible clinical signs at the doses tested.

As shown below, there was a significant difference between rats receiving CTP-692 vs D-serine with respect to markers for nephrotoxicity. At 250 mg/kg and above all rats receiving D-serine test above normal for both creatinine and BUN, while only one rat receiving CTP-692 (at 650 mg/kg) had a test value above normal for the creatinine test. This indicates that CTP-692 (vs D-serine) may translate to a reduction of nephrotoxicity in rats.



Note: Dashed line in each graph indicates upper end of normal for that assay.

* For all compound dose groups N=6 except 150mg/kg where N=12.

Conclusions

- CTP-692 and D-serine have similar intrinsic pharmacology at the NMDA receptor.
- CTP-692 is more resistant to metabolism thus higher systemic levels may be reached with the same dose.
- CTP-692 has a large %F in the preclinical species tested (rat and dog).
- CTP-692 accumulates at the site of action (forebrain) in the rat.
- CTP-692 appears less nephrotoxic in rats as measured with creatinine and BUN.

Literature cited

- Foster AB. Deuterium Isotope Effects in the Metabolism of Drugs and Xenobiotics: Implications for Drug Design. *Advances in Drug Research*, 1985;14: 1-40.
- Shao L and Hewitt MC. The Kinetic Isotope Effect in the Search for Deuterated Drugs. *Drug News & Perspectives* 2010; 23(6): 398-404.

For further information

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Presented: ACT 39th Annual Meeting, West Palm Beach, FL; Nov 4-7, 2018

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