

Combination of Peramivir and Rimantadine Demonstrate Synergistic Interaction in Influenza A Mouse Model

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Background: In the event of an influenza outbreak, two classes of antivirals, the neuraminidase (NA) inhibitors and M2 ion channel blockers, may provide valuable benefit. These anti-influenza drugs act by different mechanisms and stages of the virus replication cycle. Efficacy of combination of intramuscular (IM) administered NA inhibitor, peramivir (P), and orally administered M2 ion channel blocker, rimantadine (R), was evaluated in cell culture and mice infected with influenza A/Victoria/3/75 (H3N2) virus. **Methods:** Mice were infected with mouse adapted Influenza A/H3N2/Victoria/3/75. Peramivir was administered by IM injection, qd and rimantadine was administered orally, bid. Five day dosing began 1 hr prior to infection with virus. Each infected, drug treated group contained 9-10 mice and the saline treated group contained 15 mice. For in vitro studies, neutral red dye uptake assay was used. **Results:** Weight loss is a sensitive indicator of response to virus infection. Significant decreases in weight loss were noted in combination treated groups vs. single agent and vehicle treated groups (Table). Three dimensional analyses (MacSynergy software) of weight loss for combinations of 1mg/kg/d peramivir with 5, 10 and 30 mg/kg/d rimantadine and 3 mg/kg/d peramivir with 5, 10 and 30 mg/kg/d rimantadine demonstrated synergistic effects. In vitro combination studies with peramivir and rimantadine showed mainly additive and some synergistic effects. **Conclusion:** These data support investigation of the combination of peramivir and rimantadine for the treatment of influenza in the clinic.

Table: Effect of Combinations of Peramivir and Rimantadine on Weight Loss in Influenza A (H3N2) infected mice

Mean Weight Change @ day 10 (grams) ± SEM				
Compound (mg/kg/day)	Peramivir (P)			
	0.0	0.3	1.0	3.0
Rimantadine (R)				
0.0	-5.19 ± 0.16	-2.6 ± 0.75 ^a	-4.3 ± 0.42 ^a	-3.55 ± 0.35 ^a
5.0	-3.43 ± 0.55 ^a	-1.97 ± 0.47 ^{ab}	-1.69 ± 0.63 ^{ac}	-1.31 ± 0.34 ^{ac}
10.0	-2.1 ± 0.37 ^a	-1.25 ± 0.55 ^{ad}	-0.69 ± 0.25 ^{ac}	0.05 ± 0.22 ^{ac}
30.0	-1.64 ± 0.54 ^a	-1.52 ± 0.42 ^a	-0.41 ± 0.22 ^{ae}	0.25 ± 0.14 ^{ac}

^a p<0.05 vs. vehicle, infected; ^b p<0.05 vs. 0P/5R; ^c p<0.05 vs. either compound used alone; ^d p<0.05 vs. 0.3P/0R; ^e p<0.05 vs. 1P/0R;