

Article

Effect of Different Piperacillin-Tazobactam Dosage Regimens on Synergy of the Combination with Tobramycin against *Pseudomonas aeruginosa* for the Pharmacokinetics of Critically Ill Patients in a Dynamic Infection Model

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Supplementary materials

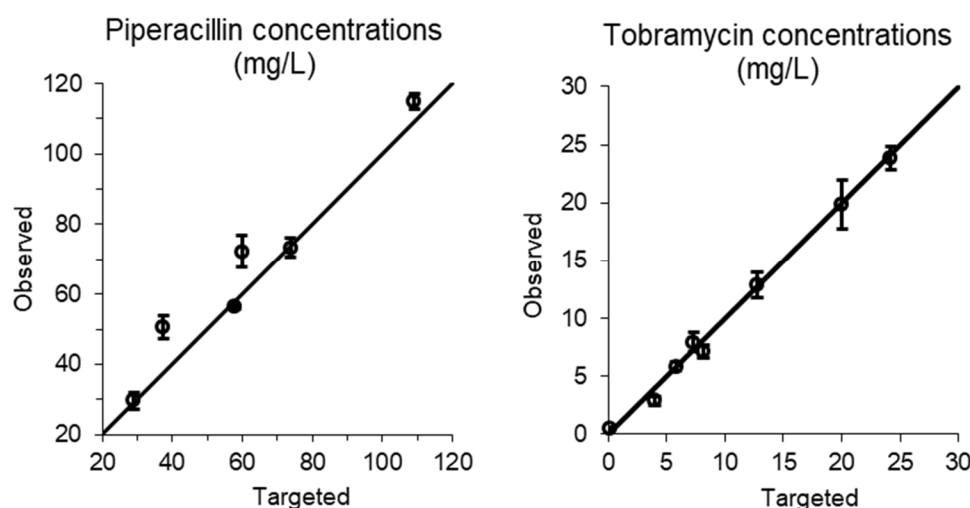


Figure S1. Observed (average \pm SE) versus targeted piperacillin and tobramycin concentrations in the dynamic in vitro infection model studies.

^a For piperacillin targeted concentrations of 29.1, 37.5, 58, 59.9, 73.8 and 109 mg/L, the number of datapoints measured were 8, 17, 40, 6, 16, and 40, respectively. For tobramycin targeted concentrations of 0.159, 4.00, 5.81, 7.32, 8.15, 12.8, 20.0, and 24.2 mg/L, the number of datapoints measured were 3, 3, 5, 5, 7, 8, 7, and 32, respectively.

Table S1. Log change for each treatment as a function of time from static-concentration time-kill studies. Treatments were either piperacillin (Pip)-tazobactam, tobramycin (Tob), or a combination, at the concentrations indicated. Blue shading indicates enhanced activity^a and green shading indicates synergy^b.

Log change [log ₁₀ (CFU _t) - log ₁₀ (CFU ₀)]																		
Isolate	Initial inoculum (log ₁₀ CFU/mL)	Time (h)	Pip 12 mg/L	Pip 24 mg/L	Pip 75 mg/L	Tob 1 mg/L	Tob 2 mg/L	Tob 8 mg/L	Pip 12 + Tob 1 mg/L	Pip 24 + Tob 1 mg/L	Pip 75 + Tob 1 mg/L	Pip 12 + Tob 2 mg/L	Pip 24 + Tob 2 mg/L	Pip 75 + Tob 2 mg/L	Pip 12 + Tob 8 mg/L	Pip 24 + Tob 8 mg/L	Pip 75 + Tob 8 mg/L	
CR382	5.99	1.5	-0.91	-0.82	-0.81	-2.24	-2.76	-4.09	-2.41	-2.56	-2.30	-2.71	-2.24	-2.85	-4.21	-3.44	-3.79	
		3	-0.52	-1.21	-1.09	-3.00	-3.76	-4.69	-3.04	-3.31	-2.82	-3.76	-3.61	-3.37	-4.99	-4.99	-5.99	
		6	-0.20	-0.94	-1.24	-2.82	-3.79	-5.99	-3.12	-3.49	-3.13	-4.29	-3.99	-4.04	-5.99	-5.99	-5.99	
		24	2.10	1.39	-1.67	2.10	-3.12	-4.39	-2.46	-2.82	-2.63	-3.37	-2.47	-2.92	-4.21	-3.99	-3.85	
		29	2.19	1.48	-1.56	2.68	-2.04	-4.69	-3.79	-3.23	-3.59	-4.99	-4.15	-4.69	-4.99	-5.99	-4.99	
		48	2.09	1.47	-1.36	3.39	3.31	-4.99	-2.67	-1.98	-3.18	-4.69	-2.52	-4.39	-5.99	-5.99	-5.99	
		72	1.70	1.24	-1.24	3.03	3.55	-5.99	-2.68	-2.58	-3.35	-5.99	-5.99	-5.99	-5.99	-4.99	-5.99	
CR382	7.38	1.5	-0.05	-0.07	-0.05	-0.25	-0.49	-2.60	-0.61	-0.60	-0.71	-1.01	-0.98	-1.10	-2.80	-2.71	-2.71	
		3	0.54	0.38	0.34	0.38	-0.63	-3.79	-0.73	-1.47	-1.60	-1.76	-2.20	-2.56	-4.26	-3.87	-3.81	
		6	0.69	0.49	0.29	0.80	-0.40	-4.25	-1.80	-2.59	-2.76	-2.47	-2.98	-3.06	-4.70	-4.28	-4.19	
		24	1.31	1.47	1.43	1.50	1.56	-1.72	1.29	0.71	-2.35	0.88	-0.36	-2.59	-3.78	-3.40	-3.17	
		29	1.28	1.68	1.51	1.49	1.05	-0.65	0.88	0.63	-1.86	0.70	-0.28	-3.34	-5.26	-5.38	-5.20	
		48	0.84	0.83	0.80	1.60	1.14	1.43	0.82	1.11	-1.58	0.35	-0.59	-1.52	-4.06	-3.82	-3.63	
		72	1.18	0.79	0.89	0.43	1.32	0.69	0.05	0.96	-1.36	1.02	-0.44	-1.43	-4.95	-4.29	-4.93	
CR379	5.87	1.5	-0.49	-0.38	-0.55	-2.10	-2.06	-3.32	-2.22	-2.08	-2.36	-2.90	-2.28	-3.19	-3.39	-3.97	-3.72	
		3	0.69	0.20	-0.38	-3.05	-4.17	-4.57	-3.51	-3.45	-4.09	-4.87	-4.87	-4.39	-5.87	-4.87	-5.87	
		6	1.07	-0.23	-2.19	-3.75	-4.57	-5.87	-3.97	-4.17	-4.39	-5.87	-5.87	-5.87	-5.87	-5.87	-5.87	

CR379	7.57	24	1.17	1.14	-2.02	2.34	-4.27	-5.87	-2.94	-3.27	-4.27	-4.57	-5.87	-4.17	-5.87	-5.87	-5.87
		29	1.66	1.12	-1.06	3.05	-3.79	-5.87	-3.39	-3.25	-3.69	-3.91	-5.87	-3.57	-5.87	-5.87	-5.87
		48	1.42	0.72	-0.74	3.14	3.01	-4.87	-1.19	-2.29	-3.64	-5.87	-5.87	-4.87	-5.87	-5.87	-5.87
		72	1.80	1.18	-0.28	3.22	3.24	-5.87	-0.19	-1.08	-3.42	-4.87	-5.87	-5.87	-5.87	-5.87	-5.87
	7.57	1.5	-0.14	-0.27	-0.23	-0.52	-1.45	-3.60	-0.82	-0.70	-0.88	-1.79	-1.71	-1.77	-3.37	-3.48	-3.46
		3	0.39	0.16	0.07	-0.62	-3.01	-4.91	-1.49	-1.90	-2.27	-3.91	-3.45	-3.70	-4.51	-4.90	-5.14
		6	0.61	0.38	0.15	0.17	-2.65	-4.82	-1.87	-3.00	-3.17	-3.50	-3.38	-3.57	-4.96	-4.89	-5.04
		24	0.19	-0.34	-0.82	1.26	1.05	-2.90	-0.01	-1.82	-2.45	-2.51	-2.60	-2.48	-3.23	-2.93	-3.05
		29	0.19	-0.79	-1.57	1.15	1.30	-5.14	0.16	-1.65	-2.66	-2.69	-2.75	-2.72	-5.67	-5.57	-5.97
		48	-0.15	-0.23	-0.95	1.18	1.34	-2.19	-0.37	-0.08	-2.44	-1.17	-1.69	-2.39	-4.30	-4.79	-5.05
		72	0.05	-0.63	-1.43	0.73	0.85	1.19	0.22	-0.05	-2.62	0.77	-1.63	-2.88	-7.57	-5.97	-5.39
								Pip 12 + Tob 1 mg/L	Pip 24 + Tob 1 mg/L	Pip 75 + Tob 1 mg/L	Pip 12 + Tob 2 mg/L	Pip 24 + Tob 2 mg/L	Pip 75 + Tob 2 mg/L	Pip 12 + Tob 8 mg/L	Pip 24 + Tob 8 mg/L	Pip 75 + Tob 8 mg/L	
CR380	5.80	1.5	-0.34	-0.46	-1.09	-1.70	-2.53	-4.20	-2.03	-2.08	-2.22	-2.74	-3.09	-3.07	-3.76	-3.90	-4.02
		3	0.26	0.01	-1.10	-2.53	-3.63	-5.80	-3.34	-2.96	-3.35	-3.35	-4.20	-4.32	-4.80	-4.80	-4.80
		6	1.93	0.83	-1.35	-3.23	-3.96	-5.80	-3.17	-3.18	-3.50	-3.85	-5.80	-5.80	-4.80	-5.80	-5.80
		24	1.80	1.31	-0.81	2.81	-1.03	-5.80	-0.84	-2.50	-2.85	-2.66	-3.48	-3.76	-4.80	-5.80	-5.80
		29	1.81	1.06	-0.78	3.31	0.13	-5.80	-0.56	-3.96	-4.50	-4.50	-5.80	-5.80	-5.80	-5.80	-5.80
		48	1.60	1.18	-0.22	3.60	3.28	-5.80	2.29	-2.81	-3.11	-3.26	-4.20	-5.80	-5.80	-5.80	-5.80
		72	1.56	1.44	0.14	2.60	2.61	-5.80	2.18	-2.96	-3.04	-3.39	-3.96	-5.80	-5.80	-5.80	-5.80
CR380	7.28	1.5	0.10	-0.15	-0.27	-1.05	-1.69	-3.04	-1.39	-1.34	-1.57	-2.06	-2.04	-2.08	-2.98	-3.15	-2.98
		3	0.25	-0.07	-0.17	-0.76	-1.96	-4.15	-1.41	-1.34	-2.06	-2.54	-2.99	-3.13	-3.54	-3.96	-3.87
		6	0.58	0.31	-0.65	0.49	-1.96	-4.44	-1.10	-1.50	-2.59	-2.76	-3.26	-3.58	-4.08	-4.19	-4.10

Pa1281		24	0.11	-0.84	-1.81	1.02	1.73	-3.44	0.47	-0.96	-2.26	-0.56	-2.84	-3.07	-3.29	-3.57	-3.68
		29	0.54	0.11	-1.39	1.79	1.77	-2.63	0.18	-0.92	-3.28	-0.18	-4.00	-4.27	-5.58	-5.38	-5.68
		48	-0.25	-0.82	-1.15	1.72	1.65	1.78	0.16	-0.54	-3.04	0.72	-3.09	-3.50	-5.58	-4.90	-4.98
		72	-0.21	-0.67	-1.28	1.51	1.89	1.84	0.26	0.32	-2.25	0.50	-1.58	-2.96	-4.59	-5.28	-5.08
	6.16	1.5	-0.11	-0.11	-0.20	-3.12	-3.75	-4.86	-3.41	-3.21	-3.80	-3.91	-4.02	-3.78	-5.16	-6.16	-5.16
		3	-1.66	-1.58	-1.76	-3.69	-4.86	-6.16	-3.96	-4.56	-4.56	-5.16	-5.16	-5.16	-6.16	-6.16	-6.16
		6	-2.69	-2.78	-3.56	-4.86	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16
		24	1.16	-0.64	-3.15	-2.02	-6.16	-6.16	-6.16	-5.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16
		29	2.05	1.25	-3.55	-0.61	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16
		48	2.55	2.05	-2.30	2.85	-0.54	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16
		72	2.81	2.65	0.25	3.06	2.20	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16	-6.16
Pa1281	7.46	1.5	0.26	0.09	-0.14	-1.62	-3.47	-4.71	-2.80	-1.66	-2.91	-3.44	-3.67	-3.88	-5.76	-6.46	-7.46
		3	0.27	0.26	0.22	-3.19	-3.89	-5.68	-4.08	-3.86	-3.93	-4.48	-4.71	-5.21	-7.46	-7.46	-7.46
		6	0.11	0.06	-0.12	-3.74	-4.89	-6.46	-4.53	-4.45	-4.64	-5.32	-5.56	-6.16	-7.46	-7.46	-7.46
		24	-0.85	-0.67	-0.75	0.99	-1.11	-7.46	-1.86	-3.62	-3.62	-5.35	-5.38	-5.16	-7.46	-7.46	-7.46
		29	-0.52	-0.46	-0.83	1.45	0.36	-7.46	-3.85	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46
		48	-0.14	-0.19	-0.49	1.60	1.36	-7.46	-0.23	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46
		72	0.42	0.41	-0.37	1.71	1.60	-4.15	1.03	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46	-7.46

Log change was calculated as change in \log_{10} CFU/mL from 0 h (CFU_0) to time t (CFU_t), where $\log \text{ change} = \log_{10} (\text{CFU}_t) - \log_{10} (\text{CFU}_0)$. ^aenhanced activity was defined as a 1 to $<2 \log_{10}$ superior killing for the combination compared to its most active component at the specified time and $\geq 2 \log_{10}$ below the initial inoculum; ^bsynergy was defined as $\geq 2 \log_{10}$ bacterial killing for the combination relative to its most active component at the specified time and $\geq 2 \log_{10}$ below the initial inoculum.