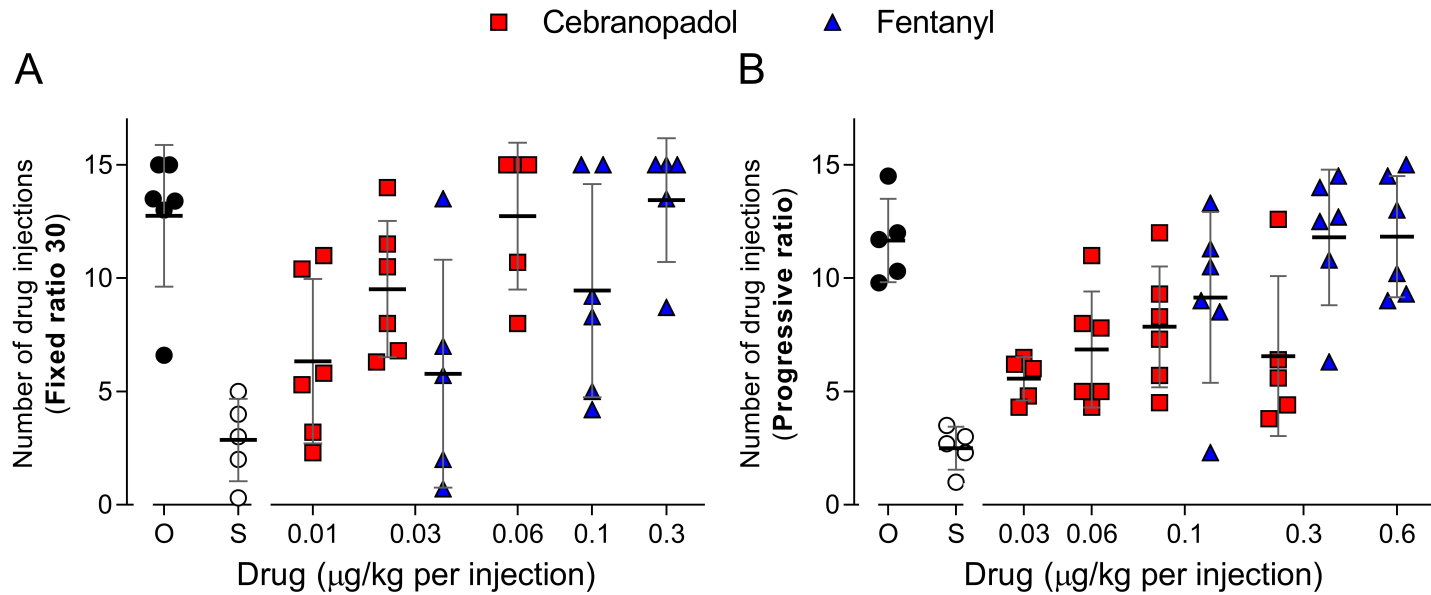
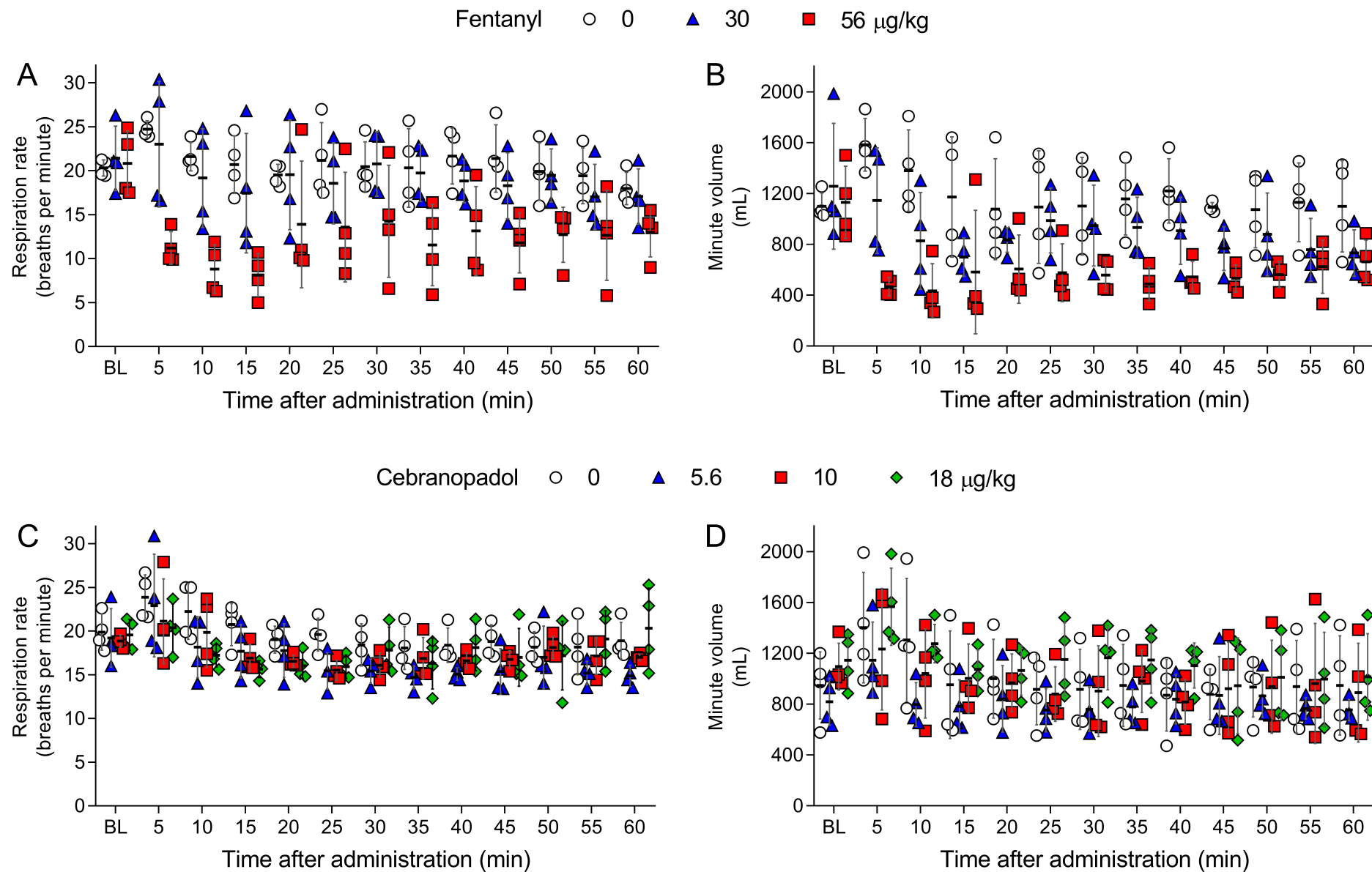


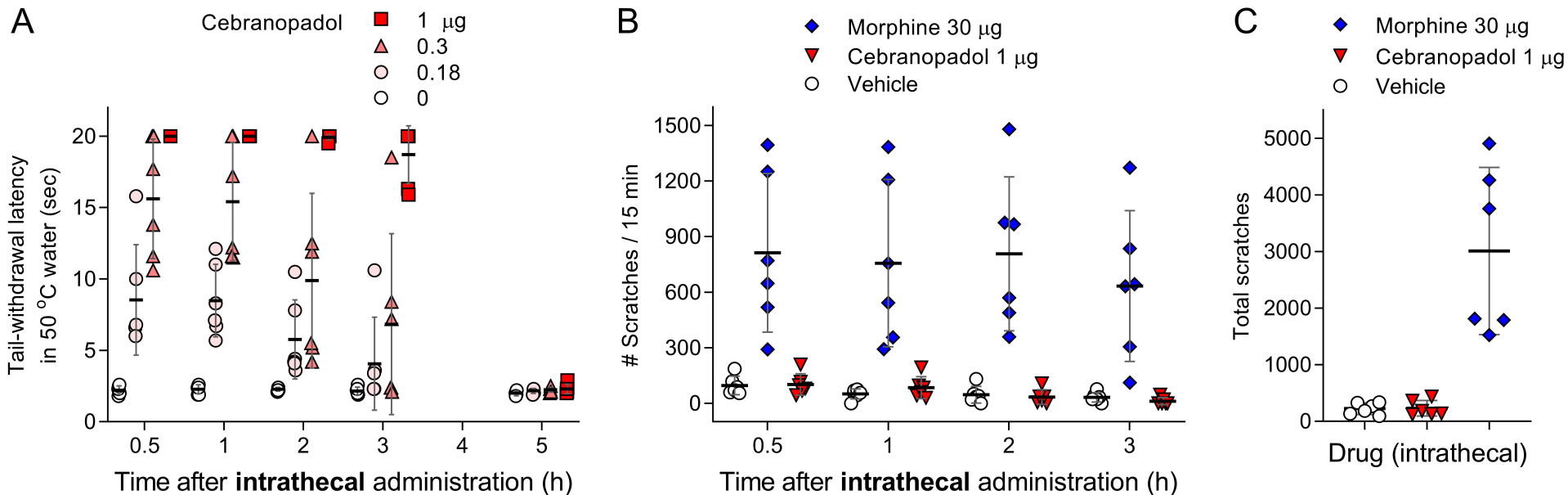
Supplemental Figure 1. Effects of systemic administration of cebranopadol on thermal nociception and itch scratching responses in monkeys. (A, B) Time courses of cebranopadol (A)- and fentanyl (B)-induced antinociception against an acute noxious stimulus (50°C water). (C) Time courses of itch scratching responses elicited by cebranopadol (5.6 $\mu\text{g/kg}$) and fentanyl (30 $\mu\text{g/kg}$) at antinociceptive doses. (D) Effects of mu receptor antagonist naltrexone (0.03 mg/kg) and nociceptin receptor antagonist J-113397 (0.1 mg/kg) on cebranopadol-induced antinociception. (E) Effects of delta receptor antagonist naltrindole (1 mg/kg) and kappa receptor antagonist 5'-guanidinonaltrindole (1 mg/kg) on cebranopadol-induced antinociception. All drugs were delivered subcutaneously. Scatter plots represent raw data from individual monkeys ($n = 4-6$) with the mean and SD imposed.



Supplemental Figure 2. Reinforcing effects of cebranopadol compared with fentanyl as measured by intravenous drug self-administration in monkeys. (A) Number of injections received as a function of dose in monkeys responding to oxycodone (O, 3 $\mu\text{g/kg}$ per injection), saline (S, ~ 0.14 mL/kg per injection), cebranopadol (0.01-0.06 $\mu\text{g/kg}$ per injection) or fentanyl (0.03-0.3 $\mu\text{g/kg}$ per injection) under a fixed ratio 30 schedule of reinforcement. (B) Number of injections received as a function of dose in monkeys responding to oxycodone (O, 3 $\mu\text{g/kg}$ per injection), saline (S, ~ 0.14 mL/kg per injection), cebranopadol (0.03-0.3 $\mu\text{g/kg}$ per injection) or fentanyl (0.1-0.6 $\mu\text{g/kg}$ per injection) under a progressive ratio schedule of reinforcement. Scatter plots represent raw data from individual monkeys ($n = 5-6$) with the mean and SD imposed.



Supplemental Figure 3. Comparison of systemic cebranopadol- and fentanyl-induced changes of respiratory parameters in freely moving monkeys implanted with telemetric probes. (A, C) Respiration rate. (B, D) Minute volume. The average value of each 5-min time block was generated from each animal to represent the measured outcome for each single data point. Both drugs were delivered intramuscularly. Scatter plots represent raw data from individual monkeys ($n=4$) with the mean and SD imposed.



Supplemental Figure 4. Effects of intrathecal administration of cebranopadol on thermal nociception and itch scratching responses in monkeys. (A) Time courses of cebranopadol-induced antinociception against an acute noxious stimulus (50°C water). (B) Time courses of itch scratching responses elicited by cebranopadol (1 μg) and morphine (30 μg) at antinociceptive doses. (C) Total number of scratches summed from the four time points shown in (B). Scatter plots represent raw data from individual monkeys (n=6) with the mean and SD imposed.