Respiratory Depressant Effects of Fentanyl Analogs


ABSTRACT

Aim: Opioid-related fatalities involving synthetic narcotics have reached unprecedented levels. This study evaluated the respiratory depressant effects of seven fentanyl analogs that have either emerged in the recreational drug marketplace or been identified in toxicological analyses following fatal or nonfatal ingestions and for which their effects on ventilation had not been previously characterized.

Methods: Adult male Swiss Webster mice (n = 8 per group) were administered fentanyl analogs [isobutyrylfentanyl, crotonylfentanyl, para-methoxyfentanyl, methoxybutyrylfentanyl, 3-fluranylfentanyl, thiofentanyl, and bezocodiolactone] via the subcutaneous route. All drugs were administered as single doses of 1, 3.2, 10 mg/kg, isobutyrylfentanyl (0.3, 1.0, 3.2, 10 mg/kg), crotonylfentanyl (0.1, 0.32, 1.32, 10 mg/kg), methoxybutyrylfentanyl (0.32, 1.32, 10 mg/kg), 3-fluranylfentanyl (0.1, 0.32, 1.32, 10 mg/kg), para-methoxyfentanyl (0.3, 1.32, 10 mg/kg), methoxybutyrylfentanyl (0.32, 1.32, 10 mg/kg), isobutyrylfentanyl (0.1, 0.32, 1.32, 10 mg/kg), and bezocodiolactone (3.2, 10, 100 mg/kg). The ED50 values for hypoventilation shown as a percentage of control are as follows: fentanyl (ED50 = 0.38 mg/kg), 3-fluranylfentanyl (ED50 = 2.60 mg/kg), crotonylfentanyl (ED50 = 7.22 mg/kg), methoxybutyrylfentanyl (ED50 = 8.54 mg/kg), isobutyrylfentanyl (ED50 = 10.35 mg/kg), crotonylfentanyl (ED50 = 18.0 mg/kg), fentanyl (ED50 = 51.6 mg/kg), and bezocodiolactone (ED50 = 181.66 mg/kg). A naloxone pretreatment (10 mg/kg) attenuated the hyperventilatory effects of all drugs.

Conclusions: These results establish that the respiratory depressant effects of these fentanyl analogs are at least in part mediated by opioid receptors.

METHODS

Whole-Body Plethysmography: Subjects were adult male Swiss Webster mice and their ventilation parameters were assessed under 5% CO2 and reverse-light dark conditions. A cumulative dosing design was employed similar to that which was previously described (1). All drugs were administered via the subcutaneous route.

RESULTS

Figure 3. Results from cumulative dose ventilation tests for analogs of fentanyl (n = 8 mice per group). Minute volume as a percentage of control (MV%CR) is shown for n = 8 mice per group. Significant differences between agonist + saline (open bars) vs agonist + 10 mg/kg naloxone (closed bars) are indicated by asterisks. ** p ≤ 0.01, *** p ≤ 0.001, **** p ≤ 0.0001. SEM: standard error of the mean.

Table 1. Results from cumulative dose ventilation tests. Efficacy estimates are expressed as %MVCR(maximum suppression as percentage of control; the smaller the percentage, the greater the suppression). t0.05% = zero suppression, 0% = complete suppression). Potency values are expressed as TD50 (mg/kg). Values for drug alone = drug potency ratio to morphine; drug potency ratio to fentanyl. Safety estimates are represented as protective indices (PI = TD50/E D). Data are mean ± SEM or 95% confidence intervals for n = 8 mice per group. SEM: standard error of the mean. TD50: half-maximal toxic dose.

Table 1. Results from cumulative dose ventilation tests. Efficacy estimates are expressed as %MVCR (maximum suppression as percentage of control; the smaller the percentage, the greater the suppression). ** p = 0.01, *** p = 0.001, **** p = 0.0001. SEM: standard error of the mean.

Figure 4. Results from cumulative dose ventilation tests for all 13 mg/kg morphine, 3.2 mg/kg buprenorphine, 3.4 mg/kg fentanyl, 10 mg/kg methoxybutyrylfentanyl, 10 mg/kg crotonylfentanyl, 10 mg/kg isobutyrylfentanyl, 10 mg/kg parame-thoxyfentanyl, 10 mg/kg napalmolactone, 3-fluranylfentanyl (3FU-FEN), and bezocodiolactone (BDX-FEN) as a percentage of control (n = 8 mice per group). Significant differences between agonist + saline vs agonist + 10 mg/kg naloxone (closed bars) condition are indicated by asterisks. ** p ≤ 0.01, *** p ≤ 0.001, **** p ≤ 0.0001. SEM: standard error of the mean.

REFERENCES


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