THE NOVEL FENTANYL-ANALOG “ACRYLFENTANYL” IMPAIRS MOTOR, SENSORIMOTOR AND CARDIOVASCULAR FUNCTIONS IN MICE
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Introduction: Synthetic opioids are a large class of new psychoactive substances (NPS) mostly consisting of analogs of fentanyl (Fen) that have caused numerous overdose and fatalities worldwide. In 2016 the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has reported a total of 130 deaths caused by a new psychoactive substance called “Acrylfentanyl” in United States and Europe. Acrylfentanyl (AcrylF) was spreading online as a research chemical, and was mostly sold in a powder or nasal spray forms. It is a potent NPS that is being used and abused causing more than 21 intoxications and 47 deaths in Europe within a relatively short time period. The aim of the present study was to compare the acute effects evoked by AcrylF, Fen and Morphine (Mor) on motor, sensorimotor and cardio-respiratory changes in mice. To better understand the pharmacological action of AcrylF, we used naloxone as opioid receptor antagonist.

Material and methods: Adult male ICR (CD-1) mice, weighing from 25 to 30 grams, were used for this experiment. We used for this study the range of doses (0.01-15mg/kg), and the three compounds were administered by intraperitoneal injection at a volume of 4ul/g. The opioid receptor antagonist naloxone (6 mg/kg, i.p.); was administered 15 minutes before AcrylF, Fen and morphine injections. The effect of AcrylF, Fen and Mor was investigated using a battery of behavioral tests widely used in studies of “safety-pharmacology” for the preclinical characterization of new molecules in rodents. All experiments were performed between 8:30 AM to 2:00 PM. Experiments were conducted in blind by trained observers working together in pairs. The behavior of mice (neurologic and sensorimotor responses) was videotaped and analyzed off-line by a different trained operator that gives test scores. Spontaneous locomotor activity was measured in four mice for each experiment where motor activity was monitored for 240 min by using the ANY-maze video-tracking system. Cardio-respiratory parameters (heart rate, breath rate, oxygen saturation and pulse distention) were measured through the software MouseOx Plus in freely moving mice, monitored by a sensor collar applied around their neck and data is recorded for 5 hours.

Results: AcrylF, Fen and Mor (0.01- 15 mg/kg i.p.), dose-dependently inhibited visual object, visual placing responses in mice. In particular, the highest dose tested (15 mg/kg i.p.) of both fentanyl drugs inhibited totally (100%) the visual responses in both tests after 10 min of injection. AcrylF induced a long-lasting analgesic effect similar to Fen but more effective at low doses than Mor. The maximal antinociceptive effect in mechanical and thermal test was reached after 35 min of injection of both fentanyl drugs. AcrylF and Fen (15 mg/kg i.p.) facilitated spontaneous motor activity, while Mor at the same dose was ineffective. All three compounds reduced heart and breath rates. AcrylF at the dose of 6 mg/kg induced a reduction of 35% of the heart rate and 30% of breath rate after 10 min of injection. The dose of 6 mg/kg of naloxone was partially effective to prevent the impairment caused by AcrylF and Fen while the same dose prevented all the effects conducted by morphine.

Discussion and conclusion: The present study demonstrates that acute administration of AcrylF markedly inhibits visual object and visual placing responses in mice, facilitates spontaneous locomotion and impairs cardio-respiratory parameters with a persistent respiratory depression in mice. Pre-treatment with naloxone was partially effective to block the effects of AcrylF and Fen. These findings support their harmful health risks and high capacity to induce fatality.