N-METHYL-2-PIRROLIDONE A POLAR ORGANIC SOLVENT IN THE DRUGS MARKET OF NPS: COMPARISON WITH GHB AND GVL IN THE MOUSE MODEL

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Introduction: The diffusion of New Psychoactive Substances (NPS) represent a global emergence that led to the need of more information and rapid analysis about these dangerous compounds. Due to their heterogeneous chemical structures, NPS were grouped in several classes, among these were detected synthetic solvent with sedative/hypnotic proprieties including NMP(N-methyl-2-pyrrolidone), GVL(G-valerolactone) and the well-known GHB (G-hydroxybutyrate). GHB was first developed for the treatment of insomnia and alcohol disorders. It has been recently reported the involvement of these substances in crime scenes more commonly sexual assault scenes (Drugs-Facilitated Sex Assault) and also in rubbery cases. The most common adverse effects declared by victims were amnesia, loss of motor control, sedation, catalepsy and respiratory depression. GVL, analogue of GBL (pro-drug of GHB), has some similarities with GHB, it recreationally used as " an excellent Valium alternative" in fact it is legally available and it has effects similar to GHB. More recently the organic solvent NMP that is widely used in the petrochemical and plastics industries,was found as a recreational drugs in two crime scenes; one was a Drug-Facilitated Sexual Assault (DFSA) and the other one was a rubbery case. The aim of this study is to evaluate and to compare the acute effects of NMP, GVL and GHB on sensorimotor (visual placing, acoustic and overall tactile responses) function, motor activity (bar and accelerod tests) and neurological functions (convulsions and myoclonus) in CD-1male mice.

Methods: Male ICR (CD-1®) mice, (25-30 gr) were group-housed 8to 10 mice per cage. Drugs were initially dissolved in saline (0.9% p/v NaCl) and were administered by gastric gavage at a volume of 4ul/gr. The range of doses used for this study was 100 mg/kg to 3000 mg/kg. The effect of NMP, GVL and GHB 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.

Results: Gavage administration of NMP, GVL and GHB (100-3000mg/kg i.p.) caused behavioural and physiologically alterations in mice. The administration of these compounds reduced sensorimotor functions (visual placing, acoustic and overall tactile responses) in a dose-dependent manner. In particular, GHB deeply impaired sensorimotor response at 400 mg/kg yet, GVL had maximal effect only the highest dose injected (3000 mg/kg i.p.), while NMP at the same dose partially inhibited sensorimotor function. Moreover, all the animals have developed neurological impairments including handling-induce seizure and myoclonus at higher doses tested. Similarly all the three solvents caused a marked catalepsy and the GHB was the more potent compound showing important effects at low doses. In fact, GHB at 200 mg/kg in the bar test showed a marked catalepsy while GVL and NMP induced cataleptic state. In the accelerod test the three solvents at the dose of 100 mg/kg increased locomotion, while the higher doses reduced the animal motor performances. Regarding physiologically alterations, all the solvent caused hypothermia and respiratory depression. In particularly, GHB caused at elevated doses (2000-3000 mg/kg i.p.) a marked respiratory depression, gasping and the death of all mice treatrd. GVL induced respiratory depression and death of all mice only at the highest dose tested (3000mg/kg i.p.). NMP was less effective in respiratory alterations compared to the other molecules and did not cause mice death. All substances induced a marked hypothermia where GHB is again more potent than GVL and NMP.

Discussion and conclusion: For the first time, the present study reports the pharmaco-toxicological effect of NMP in comparison with other (GHB and GVL) sedative/hypnotic solvents in mice. All the three compounds, dose-dependently reduced visual placing, acoustic and tactile responses, impaired motor responses. The gavage administration of GVL and GHB induced seizure handling-induce, myoclonus and high respiratory depression that caused the death of all mice. The pharmaco-toxicological comparison of the effects induced by NMP, GVL and GHB showed that GHB is the most potent and effective to induce intoxication in mice suggesting the high risks that these solvents could cause for public health.