WG 1 (Chemical, Biological, Radiological and Nuclear materials)

Delayed Combined Antiseizure Medications Levetiracetam, Ketamine, and Midazolam Reduces Sarin-Induced Seizure Activity and Brain Damage in the Rat Model

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The development of refractory status epilepticus (SE) following sarin intoxication presents a therapeutic challenge. In this current research we evaluated the efficacy of a delayed combined double or triple treatment in reducing the abnormal electrographic seizure activity (ESA) and ensuing long-term neuronal insult. SE was induced in rats by exposure to 1.2LD50 sarin followed by treatment with atropine and TMB4 (TA) 1 min later. Double treatment of ketamine and midazolam or a triple treatment of ketamine, midazolam and levetiracetam was administered 30 min post exposure and was compared to a delayed single treatment with midazolam alone or to the triple treatment of ketamine, midazolam, and valproate, which was shown previously to ameliorate this neuro-insult. Toxicity and electrocorticogram activity were monitored during the first week, and behavioral evaluation was performed 3 weeks post exposure followed by biochemical and immunohistopathological analyses. The triple and to less extent the double treatment significantly ameliorated the duration and intensity of the seizures and the ESA. Both treatments reduced the sarin-induced increase in the neuroinflammatory marker PGE2, the brain damage marker TSPO, decreased gliosis, astrocytosis and neuronal damage compared to the TA only or TA + midazolam treated groups. Finally, both double and triple treatments prevented behavioral impairment using the open field test. The delayed double and to more extent triple treatment may serve as an efficient delayed therapy, which prevents brain insult propagation following sarin-induced refractory SE.

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Treating High Dose Fentanyl and Carfentanil Intoxication

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Synthetic opioids, such as fentanyl, are widely used to manage chronic and severe pain. Over recent decades, fentanyl and some of its analogs, such as carfentanil, have become increasingly prevalent among drug users. The relative ease of synthesis and the growing prevalence of these drugs pose a significant threat, as they could potentially be used as chemical agents in terror attacks against civilian population. These compounds can be fatal in relatively small amounts.

Aims:

1. To evaluate and compare the efficacy of i.m. and i.v. naloxone administration for the treatment of high dose fentanyl and carfentanil intoxication.
2. To assess the efficacy of i.m. antidotal treatment with naltrexone and nalmefene in counteracting fentanyl and carfentanil intoxication and in preventing re-narcotization.

Methods:

Rabbits were administered varying doses of naloxone at different time points (20, 60, 120 sec) following i.v. injection of high doses of fentanyl or carfentanil. Naloxone was administered by either i.v. or i.m. route, protection factor was calculated and the efficacy of each injection method was determined. Additionally, the efficacy of i.m. naltrexone and nalmefene treatments against fentanyl and carfentanil intoxication was evaluated in rabbit and rats.

Results:

All rabbits and rats exhibited typical symptoms of opioid intoxication that started within seconds of fentanyl or carfentanil injection. Symptoms included stretching, opisthotonos, breathing distress, loss of righting reflex and loss of corneal reflex, loss of consciousness and in some cases, apnea and death.

Naloxone treatment was highly effective as long as it was administered within 1 minute following intoxication. Both, the i.m. and the i.v. routes afforded high protection, yet the i.v. route was more effective, allowing longer delay between intoxication and treatment.

Both, naltrexone and nalmefene also provided high protection, with efficacy comparable to naloxone in the rabbit model and proved to decrease and even eliminate occurrence of re-narcotization.

Conclusions:

The results of these experiments clearly indicated that i.m. antidotal treatments with naloxone as well as naltrexone or nalmefene are very effective against both, fentanyl and carfentanil high dose intoxication, provided treatment is initiated immediately after intoxication. These findings highlight the need for readily available automatic autoinjectors these antidotes, particularly for use by first responders.