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Ketamine combinations for the field treatment of soman-induced self-sustaining *status epilepticus*. Review of current data and perspectives ☆

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ABSTRACT

Organophosphorus nerve agents (NA), potent irreversible cholinesterase inhibitors, could induce severe seizures, *status epilepticus* (SE), seizure-related brain damage (SRBD) and lethality. Despite the lack of data in the case of NA, clinical evidences suggest that SE survivors could suffer from neurological/cognitive deficits and impairments such as spontaneous recurrent seizures (epilepsy) after a latent period of epileptogenesis. It is beyond doubt that an effective and quick management of the initial seizures and prevention of SRBD are critical to prevent these long-term consequences, explaining why most experimental data are focusing on the 5–40 min post-exposure time frame. However, in field conditions, treatment may be delayed and with the exception of NMDA receptor antagonists, currently no drug provides protection (against lethality, seizures, SRBD and neurological consequences) when seizures are left unabated for one hour or more. Ketamine (KET) is the only NMDA antagonist licensed as an injectable drug in different countries and remains an anesthetic of choice in some difficult field conditions. In this short review paper, after a presentation of some of the key points of the pathophysiology of NA-induced SE and a quick survey of the potential therapeutic avenues in the context of delayed treatment of NA-induced SE, we will review the recent data we obtained showing that KET, in combination with atropine sulfate (AS), with or without a benzodiazepine, considerably reduces soman-induced neuroinflammation, provides neuroprotection, histologically and functionally, and also positively modify soman-induced changes in brain metabolism. Finally, we will also mention some results from safety studies including those bringing evidence that, at difference with MK-801, KET does not impair thermoregulation and even seems to reduce AS-induced heat stress. All in all, KET, in combination, appears a good candidate for the out-of-hospital treatment of severe NA-induced SE.

1. Introduction

In the chemical warfare arsenal, the organophosphorus (OP) nerve agents (NA) are the most dangerous agents known. These compounds are a threat during some combat situations (e.g. Iran–Iraq war (1980–1988) and the second Gulf war in 1991), and are feared during terrorist attacks if terrorists were to acquire this capability (Japan, 1994–1995). NA act as potent irreversible inhibitors of cholinesterases (ChEs) in both central (CNS) and peripheral nervous systems and induce an immediate hypercholinergic crisis responsible for most of the initial pathological responses to the poisoning. Several NA are known but soman (pinacolyl methyl phosphonofluoridate) is considered a major threat, because of known existing stockpile and because of the difficulty in treating poisoning owing to a very rapid aging reaction. Depending upon the dose, exposure to NA such as soman can produce hypersalivation, lacrimation, relaxation of sphincters, respiratory distress, cardiovascular dysfunction, coma and rapid death [1]. During intoxications with high sub-lethal to lethal doses of NA, the excess of acetylcholine in the brain triggers seizures and leads to the secondary recruitment of the excitatory glutamate (Glu) system [2]. Through overstimulation of Glu receptors, including the ionotropic *N*-methyl-D-aspartate (NMDA) receptors, Glu is thought to play a prominent role in the long-lasting maintenance of seizure activity (*status epilepticus*, SE) and in the build-up of seizure-related brain damage (SRBD) [3,4]. Ketamine (KET) is an NMDA antagonist of clinical use in many areas of medicine, from

☆ All the experimental protocols were approved by either the DRDC Suffield or the CRSSA Animal Care and Use Committee and all procedures were conducted in accordance with appropriate regulations in accredited research facilities.

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[1] Dr. Pierre Carpentier, a world-renown specialist of nerve agent-induced brain damage and related medical counter-measures, sadly passed away on the 23rd of August. He will be greatly missed by his family and colleagues.

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anesthesia, pain management and more recently, depression. In this paper, after a brief presentation of some of the key points of the pathophysiology of NA-induced SE and a quick survey of the potential therapeutic avenues in the context of delayed treatment of NA-induced SE, we will review the data we obtained over the recent years showing that KET, administered during SE in combination with atropine sulfate (AS), with or without a benzodiazepine (BZD), considerably reduces soman-induced neuroinflammation, provides neuroprotection, histologically and functionally, and also positively modifies soman-induced changes in brain metabolism. Finally, we will also mention some results from safety studies.

2. Seizures, *status epilepticus* and brain damage following nerve agent poisoning – pharmacological management of SE, SSSE/RSE

Although SE was traditionally defined as a single clinical seizure lasting more than 30 min or repeated seizures over a period of more than 30 min without intervening of consciousness, the duration of continuous seizures has been now reduced to 5 min [5]. SE then may become self-sustaining (SSSE) [6]. SE will also become refractory to standard treatment, especially to BZD. Refractory SE (RSE) thus describes continuing SE despite adequate initial pharmacological treatment with first- and second-line anticonvulsant drugs such as BZD, phenytoins, valproate and derivatives, and Phenobarbital [7–14]. Levetiracetam is also now sometimes used with success. It may be interesting in the case of soman-induced seizures in combination [15]. In more general terms, whatever the cause, SE is an under-recognized medical emergency that requires rapid and aggressive treatment to prevent neuronal damage, systemic complications and death. Like any other generalized convulsive SE, NA-induced SE will be accompanied by seizure-related brain damage (SRBD) if full-blown seizures are left unabated [3,4,16–18]. It is generally thought that soman-induced SRBD is mainly due to the unregulated activity of the excitatory neurotransmitter Glu on its different receptors, either metabotropic [19], or ionotropic, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors [20] or NMDA receptors. There is a general agreement that the latter play a key role in mediating at least some aspects of Glu neurotoxicity. Oxidative stress [21], neuroinflammation (e.g. [22–24] and references therein) and changes in brain metabolism [25,26] are part of the picture. Long-term neurological sequelae will include cognitive deficits (e.g. [27–30]) as well as probably epilepsy as reported with other animal models of seizures. NA-induced epileptogenesis has never been addressed comprehensively despite the fact that recurrent seizures are known to occur [31], even after treatment [32]. Unfortunately, long-term electroencephalogram (EEG) surveillance or behavioral studies are often lacking in studies on neuroprotectants, thus precluding from fully evaluating the real protection afforded, beyond simple histology obtained during the acute phase.

There is no doubt about the paramount importance of an effective and timely administration of anticonvulsants at a very early stage (if possible before the first 15–20 min) after poisoning to avoid SRBD and cognitive deficits and most of the teams have focused over the years on this time frame. However, in the aftermath of a military or a terrorist attack, disorganisation and operational constraints will also delay medical evacuation, medical diagnosis and management of SE. This will lead to a necessary, but extremely challenging, out-of-hospital management of SE and SSSE/RSE. Drug combinations are generally required (e.g. [33,34]) as a single drug acting as a 'magic bullet' probably does not exist. A review of the literature shows that there are very few drugs, or drug combinations, able to stop NA-induced SE and/or be neuroprotective after 30–40 min of seizures. At present, the noncompetitive antagonists of NMDA receptors hold out a great promise for the treatment of soman-induced SE in the 40+ min time frame, even up to 3 h in some instances: MK-801, dizocilpine [4,35–38], TCP [16,39–41] or GK-11, gacyclidine [42–45] (for a more detailed review, see [46]). KET hydrochloride is marketed as a short-acting, general anesthetic for human and veterinary use. KET differs in several aspects from other anesthetics and its properties have been recently reviewed (e.g. [47,48]), especially considering its potential use in NA poisoning [46,49]. KET is not fully selective for NMDA receptors and it displays other pharmacological effects [48], the real importance of which is not entirely understood, especially if KET is to be used after NA intoxication. This review is too short to cite all current clinical applications of KET, especially in prehospital settings and difficult environments, owing to its cardiovascular and respiratory favorable features and anesthetic and analgesic properties (e.g. [50–56]). KET antiepileptic and neuroprotective activities have been evaluated in different experimental seizure models (for a review see [46]). KET is often missing from the clinical recommendations or reviews (e.g. [8]) or the published doses are erroneous (e.g. anesthetic dose for rodents [9]). Nonetheless, KET is now proposed by some authors as a possible (third-line) treatment for RSE, often in combinations [6,7,9,10,57,58].

3. Treatment of severe soman poisoning by ketamine combinations

3.1. Efficacy studies in poisoned animals

3.1.1. Efficacy studies in guinea-pigs

Because of the earlier work we performed on NMDA antagonists (TCP and GK-11) [16,39,40,42–44], we naturally became interested in KET, the only commercially available injectable NMDA antagonist licensed for human use. Early attempts to evaluate KET during soman-induced seizures failed to find any beneficial effects of a single low dose of KET, injected very early after challenge [59]. Since NMDA receptor antagonists usually prove more efficient when administered later in the course of seizures [40,43,60], new experiments were then undertaken [32,61] in which KET, or S(+)-KET, were repeatedly administered every 30 min in association with AS to guinea-pigs poisoned by $2 \times LD_{50}$ of soman. Repeated injections of KET appeared necessary because of the known short action of the drug. Animals were intoxicated in the presence of pyridostigmine and methylatropine nitrate (a peripherally-acting antimuscarinic) to ensure sufficient survival and thus observation of long-lasting seizures. All control animals died within 24 h. The sub-anesthetic dose regimen (10 mg/kg, 6 times with 2 mg/kg AS) fully protected the animals against soman-induced lethality when administration started 30 min after challenge. The low-dose regimen was also able to fully arrest seizures during the period of observation (8 h post-challenge). At least two injections were usually necessary. Recurrence of short epileptic fits on the following day was not totally prevented. Along with seizure control, brain was very efficiently protected, as judged by hemalun–phloxine staining. The efficacy of the combination was greatly reduced when the first injection was delayed to 60 min. In contrast, increasing the KET dose to anesthetic levels (40–60 mg/kg in the guinea pig) was successful at this delayed time point. A single injection of 60 mg/kg KET with 10 mg/kg AS could significantly improve survival of the animals compared to soman controls but did not fully prevent the recurrence of seizures during the period of observation. In order to improve the outcome, multiple injections of either 40 or 60 mg/kg KET were thus also evaluated. Two injections of 60 mg/kg KET or three injections of 40 and 60 mg/kg significantly improved survival compared to the soman control group. Seizures were abated within 10 min following the first injection of 40 or