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Evaluation of the Anticonvulsant Gabapentin against Nerve Agent-Induced Seizures in a Guinea Pig Model

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14. ABSTRACT Gabapentin is an anticonvulsant drug approved by the FDA as an adjunctive medication to control partial seizures, and recently has been approved for treating neuropathic pain. This study evaluated whether gabapentin could terminate or moderate nerve agent-induced seizures using a validated guinea pig model. Male Hartley guinea pigs were surgically prepared to record electroencephalographic (EEG) activity. After a week recovery, animals were pretreated with pyridostigmine 30 min prior to subcutaneous soman challenge (56 ug/kg; 2 X LD50). One min later, animals were administered atropine sulfate + 2-pralidoxime chloride. EEG activity was recorded continuously for 5 hr after exposure and 30 min the next day. This regimen elicits status epilepticus seizures in 100% of animals with a latency of ~7 min. Gabapentin in doses from 3.2 – 180.0 mg/kg failed to control seizure activity when administered as a therapy at seizure onset. When given as a pretreatment 30 min before soman exposure, seizures were prevented or suppressed in a dose-dependent fashion. Gabapentin possesses some anticonvulsant properties against these seizures when administered as a pretreatment, but high dose requirements and potential side effects make this impractical. Gabapentin and compounds of this class show little promise as a replacement treatment for nerve agent-induced seizures.					
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Abstract

Gabapentin is an anticonvulsant drug that was originally approved by the FDA as an adjunctive medication to control partial seizures, and recently it has additionally been approved for treating neuropathic pain such as that associated with shingles. Gabapentin prevents seizures as do other anticonvulsants. in animal test systems designed to detect anticonvulsant activity, but the mechanism by which gabapentin exerts its anticonvulsant action is unknown. Gabapentin has been reported to moderate *status epilepticus* seizures induced by high doses of pilocarpine. The present study evaluated whether gabapentin could terminate or moderate nerve agent-induced seizures using a validated guinea pig model. Male Hartley guinea pigs were surgically prepared with cortical screw electrodes to record brain electroencephalographic (EEG) activity. After a week of recovery, animals were pretreated with pyridostigmine (0.026 mg/kg) intramuscularly (IM) 30 min prior to subcutaneous (SC) challenge with soman (56 ug/kg; 2 X LD50). One min after soman challenge, the animals were administered atropine sulfate (2.0 mg/kg, IM) + 2-pralidoxime chloride (2-PAM Cl, 25 mg/kg, IM). EEG activity was recorded continuously for at least 5 hr after exposure and 30 min the next day. This treatment regimen elicits status epilepticus seizures in 100% of treated animals with a latency of ~7 min after soman exposure. Gabapentin in doses from 3.2 – 180.0 mg/kg failed to control seizure activity when the drug was administered as a therapy immediately at seizure onset. In contrast, when gabapentin was given as a pretreatment 30 min before soman exposure, seizures were prevented or suppressed in an apparent dose-dependent fashion (1 of 6 animals at 100 mg/kg; 2 of 6 animals at 180 mg/kg; 3 of 6 animals at 320 mg/kg). Based on these results, it can be concluded that gabapentin is not capable of stopping nerve agent-induced seizures when the drug is administered therapeutically as would be the typical case in a military situation. Gabapentin does possess some anticonvulsant properties against nerve agent-induced seizures when administered as a pretreatment, but the high dose requirements and the potential side effects make this an impractical option. Gabapentin and other compounds of this class (e.g., pregabalin) show little promise as a replacement treatment for nerve agent-induced seizures.

Introduction

Nerve agent-induced seizures result from overstimulation of susceptible brain circuits by abnormally high levels of the excitatory neurotransmitter acetylcholine, which rapidly builds up after inhibition of the enzyme acetylcholinesterase by nerve agent (McDonough and Shih, 1997). These seizures, unless quickly stopped pharmacologically, rapidly progress to a state known medically as *status epilepticus*, and if the seizures persist long enough they can produce brain pathology (Carpentier et al., 1990; McDonough et al., 1995; McDonough and Shih, 1997; Tonduli et al., 1999). Due to the difficulty in treating nerve agent-induced seizures there has been an ongoing effort to determine if there are better anticonvulsants to control these seizures. Previous work (Shih et al., 1991, 1999; McDonough et al., 2004) has shown that most antiepileptic drugs used to treat seizure disorders are ineffective in controlling nerve agent-induced seizures. This is possibly because most anticonvulsant drugs are taken to prevent the development of seizure activity in epileptic patients rather than to stop ongoing seizure activity such as occurs in nerve agent poisoning. However, new anticonvulsants are constantly being developed with different mechanisms of action, and these compounds need to be systematically evaluated for anticonvulsant effects against nerve agent-induced seizures.

Gabapentin, whose chemical structure is displayed in Figure 1, is a relatively new clinically used antiepileptic drug that was originally approved as an adjunctive medication to control partial seizures. More recently it has received an additional indication for treating neuropathic pain. It is marketed under the name Neurontin[®]. Gabapentin prevents seizures as do other marketed anticonvulsants in animal test systems designed to detect anticonvulsant activity, but the mechanism by which gabapentin exerts its anticonvulsant action is unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA), but it does not interact with GABA receptors. It is not converted metabolically into GABA nor does it act as a GABA agonist, and it is not an inhibitor of GABA reuptake or degradation. *In vitro* studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain, including the neocortex and hippocampus. The identity and function of this binding site remain to be elucidated. Its therapeutic action in neuropathic pain is thought to be due to binding at the $\alpha 2\delta$ subunit of voltage-dependent calcium channels in the central nervous system, thereby inhibiting channel trafficking and plasma membrane expression (Hendrich et al., 2008).

There are two reports that gabapentin, when given as a pretreatment, is capable of modulating pilocarpine-induced seizures, which are considered by some to be similar to nerve agent-induced seizures (Freitas et al., 2006; Pereira et al., 2007). Gabapentin is one of the few clinically used antiepileptic drugs that has not been evaluated as a potential anticonvulsant against nerve agent-induced seizures. The current study examined whether gabapentin would be capable of stopping or modulating nerve agent-induced seizures in a validated guinea pig nerve agent seizure-anticonvulsant model (Shih et al., 2003, 2007; McDonough et al., 1999, 2000, 2004, 2008).

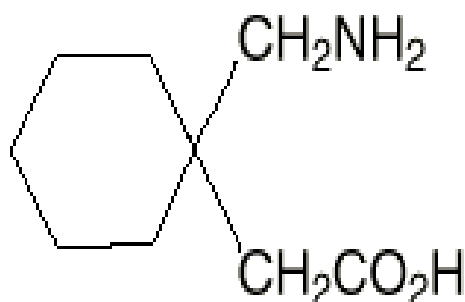


Figure 1. Chemical structure of gabapentin.

Materials and Methods

Subjects: Male Hartley guinea pigs (Crl:(HA) BR COBS; Charles River Labs, Kingston, NY), weighing 250-300 g before surgery, served as subjects. They were individually housed in temperature ($21 \pm 2^\circ \text{C}$) and humidity ($50 \pm 10\%$) controlled quarters that were maintained on a 12-hr light-dark cycle (lights on at 0600) and received food and water ad libitum except during the ~6 hr experimental period in the recording chambers.

Surgery: Approximately one week before experimentation the animals were implanted with stainless-steel cortical screw electrodes to record electroencephalographic (EEG) signals. The animals were anesthetized with isoflurane (3% induction, 1.5-2% maintenance; with oxygen) and set in a stereotaxic frame. Three cortical stainless-steel screw electrodes were implanted in the skull: two were placed bilaterally ~3.0 mm from the midline and equidistant between bregma and lambda; the third was placed on the posterior calvarium as the reference electrode. Stainless-steel wires attached the screws to a miniature connector plug. The electrodes, wires and plug were encased in cranioplastic cement. The incision was sutured; the animal was removed from the frame, given the analgesic buprenorphine HCl (0.03 mg/kg, SC) and placed on a warming pad for at least 30 min before being returned to the animal quarters.

Materials: Saline (0.9% NaCl) injection, USP, and sterile water for injection were purchased from Cutter Labs, Inc. (Berkeley, CA). Pyridostigmine bromide was obtained from Hoffmann-La Roche, Inc. (Nutley, NJ), and pyridine-2-aldoxime methylchloride (2-PAM) was purchased from Ayerst Labs, Inc. (New York, NY). Atropine sulfate (USP) and gabapentin were purchased from Sigma-Aldrich Chemical Company (St. Louis, MO). (Note: Gabapentin, though available commercially, was not available in a USP formulation for systemic administration). AttaneTM (isoflurane, USP) was purchased from Minrad, Inc. (Bethlehem, PA). Buprenorphine HCl was purchased from Reckitt Benckiser Pharmaceuticals, Inc. (Richmond, VA). The nerve agent soman was obtained from the US Army Edgewood Chemical Biological Center (Aberdeen Proving Ground, MD).

Pyridostigmine bromide was prepared in sterile water to a concentration of 0.052 mg/ml. Atropine sulfate (4 mg/ml) and 2-PAM (50 mg/ml) were prepared in saline as an admixture and administered 0.5 ml/kg. Soman was prepared in ice cold saline to a concentration of 112 ug/ml. Gabapentin was diluted in saline to varying concentrations that delivered 1 ml/kg.

Procedures: Animals were tested in squads of eight on a given study day. They were randomly assigned to a treatment condition and dose group. The animals were weighed and placed in a recording chamber, and at least 15 min of baseline EEG was recorded. EEGs were recorded using CED 1902 amplifiers and displayed on a computer running Spike2 software (Cambridge Electronic Design, Ltd., Cambridge, UK). The animals were then administered 0.026 mg/kg pyridostigmine IM, a dose determined to produce ~30% whole blood cholinesterase inhibition (Lennox et al., 1985). This dose of pyridostigmine never produced any abnormal behavior in the animals, nor changed the appearance or waveform characteristics of the EEG as measured by power spectral analysis prior to administration of soman. Thirty min after pyridostigmine the animals were challenged SC with 56 ug/kg soman (2 X LD50) and one min later were treated IM with the admixed 2.0 mg/kg atropine and 25.0 mg/kg 2-PAM. This procedure results in seizures in 100% of animals tested in multiple studies (McDonough et al., 1999, 2000, 2004; Capacio et al., 2003, 2004). The animals were then monitored for seizure onset by a technician and the investigator, who were well-experienced with the appearance of nerve agent-induced EEG seizure activity in guinea pigs. Seizure onset was operationally defined as the appearance of >10 sec of rhythmic high amplitude spikes or sharp waves that were at least twice the baseline amplitude. In the first study, animals were treated with gabapentin (10, 100, or 180 mg/kg, IM) as therapy immediately after the appearance of epileptiform seizure activity in the EEG record. In the second study, gabapentin (100, 180 or 320 mg/kg, IM) was given as a pretreatment 30 min before soman exposure and immediately after administering pyridostigmine pretreatment. The EEG was continuously monitored for at least 5 hr after soman exposure and for 30 min at 24 hr after exposure. At the end of the EEG recording on the exposure day, the animals were returned to the animal quarters where food and water were freely available. Each animal was rated as having the seizure terminated (first study, gabapentin as therapy) or never developed (second study, gabapentin as pretreatment) or not terminated based on the overall appearance of the EEG record at the end of the experimental day and during the 24-hr recording. Evaluation and categorization of the EEG response by an individual animal to treatment were performed by a technician and investigator, both well-experienced with the appearance of nerve agent-induced EEG seizure activity. The overall rating and timing of different events required consensus between both individuals, who were aware of the treatment conditions of an individual animal. To be rated as having the seizure terminated or prevented, all spiking and/or rhythmic waves had to stop or never appear and the EEG had to remain normal at all subsequent observation times (n.b., throughout the 5-hr record following exposure and for the 30-min record 24 hr later). For each animal in which the seizure was terminated, the latency to seizure termination was measured as the time from when the animal received gabapentin treatment to the last observable epileptiform event in the EEG. These evaluation procedures and operational criteria for seizure control are identical to those used in previous studies utilizing this animal model (McDonough et al., 1999, 2000, 2004; Capacio et al., 2003, 2004; Shih et al., 2003, 2007).

Results

In the first study, gabapentin, given as a therapy treatment after the onset of soman-induced seizures, was unable to stop these seizures at the doses (10, 100, 180 mg/kg) tested. These data are presented in Table 1. When it was given as a therapy, gabapentin did moderate the electrographic seizure activity by reducing the amplitude of the seizures, as can be seen in Figure 2, but it did not terminate seizure activity, as has been observed with effective anticonvulsants using this model.

Table 1. The lack of anticonvulsant effect of gabapentin on soman-induced seizures when given as a treatment immediately after seizure onset.

Gabapentin Dose	Seizure Off/Number Tested	24-hr Survival/Number Tested
10 mg/kg	0/2	0/2
100 mg/kg	0/6	2/6
180 mg/kg	0/3	3/3

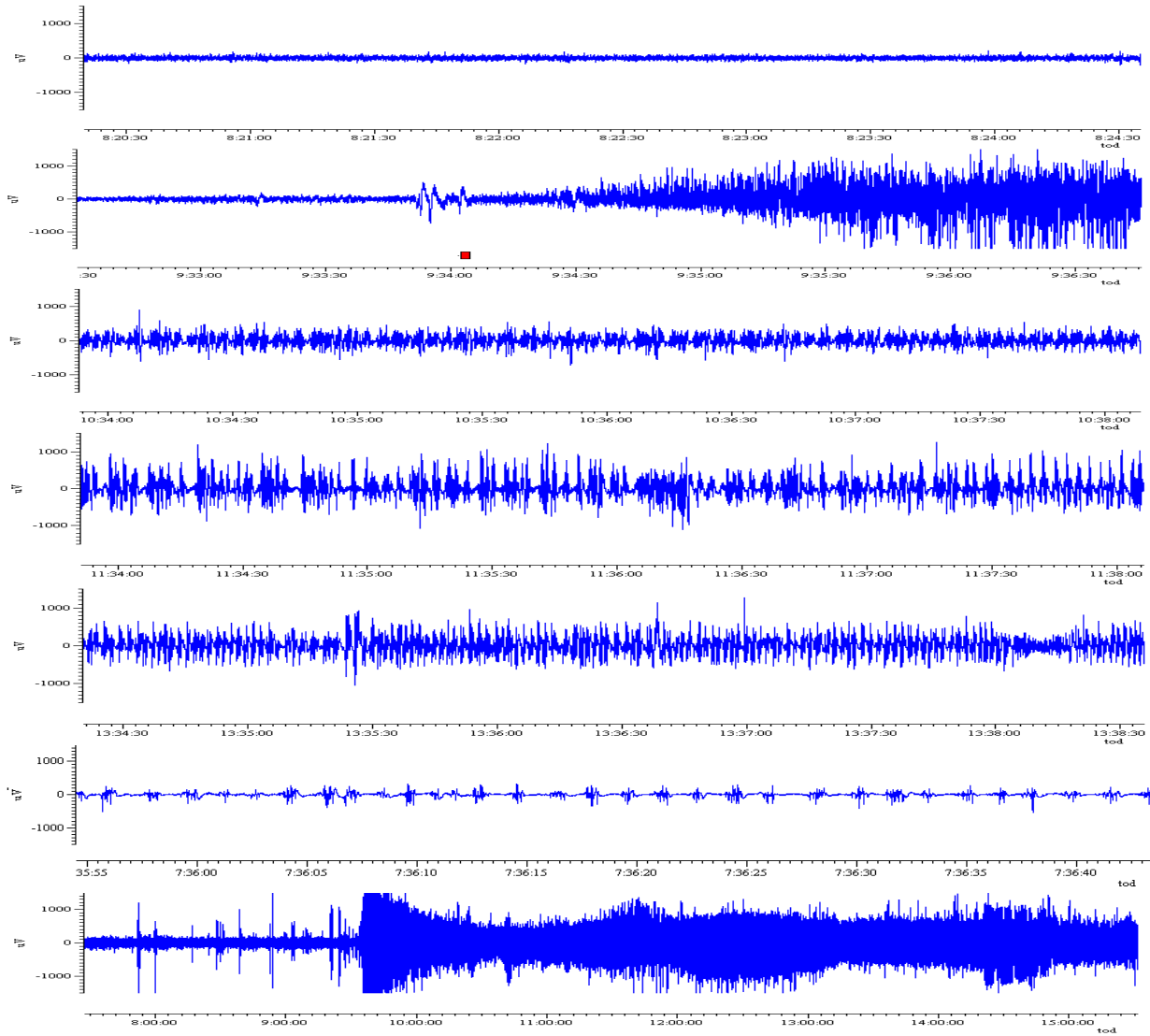


Figure 2. Example of the EEG response of one guinea pig to soman exposure and treatment with 180 mg/kg, IM, gabapentin at seizure onset. The top five strips show a progression of 4-min epochs of EEG from various phases of the experiment for this animal; top strip is baseline EEG before soman exposure; second strip shows seizure onset approximately 6 min after soman injection; gabapentin (180 mg/kg) was given at the event mark as denoted by the red square; the next three strips show records at 1, 2 and 4 hr, respectively, after gabapentin treatment. Note that high amplitude epileptiform activity persisted throughout this time. Next to bottom strip shows a one-min EEG epoch approximately 22 hr after exposure; the amplitude of the seizure is much diminished, but note the periodic epileptiform discharges that dominate the record. Bottom strip shows the 8-hr compressed record of the EEG

response of this animal; note the large increase in EEG amplitude following soman. This diminished somewhat after gabapentin treatment, but overall it stayed significantly elevated throughout the remainder of the day.

When given as a pretreatment 30 min before soman exposure, gabapentin prevented seizures from occurring in a dose-dependent fashion. These data are presented in Table 2. Probit analysis showed that gabapentin possessed an anticonvulsant $ED_{50} = 310.9$ mg/kg for preventing soman-induced seizures under these conditions. An idealized anticonvulsant dose-effect curve based on these data is presented in Figure 3. However, statistically the dose-effect curve was not significant, and confidence limits for the ED_{50} could not be calculated. Two of the animals treated with 180 mg/kg gabapentin actually developed brief periods of low amplitude spiking. This spiking stopped after 1 min 50 sec in one animal, and that animal was seizure free through all the rest of the recordings. The other animal displayed ~3 min of spiking, but continued to show bouts of elevated slow waves the rest of the day and had a normal EEG at 24 hr. The animals that responded to gabapentin in the 100 mg/kg (1 of 6) and 320 mg/kg (3 of 6) dose groups were judged never to have developed seizures.

Table 2. Gabapentin prevented seizure development when given as a pretreatment 30 min before soman exposure.

Gabapentin Dose	Seizure Off/Number Tested	24-hr Survival/Number Tested
100 mg/kg	1/6	2/6
180 mg/kg	2/6	3/6
320 mg/kg	3/6	5/6

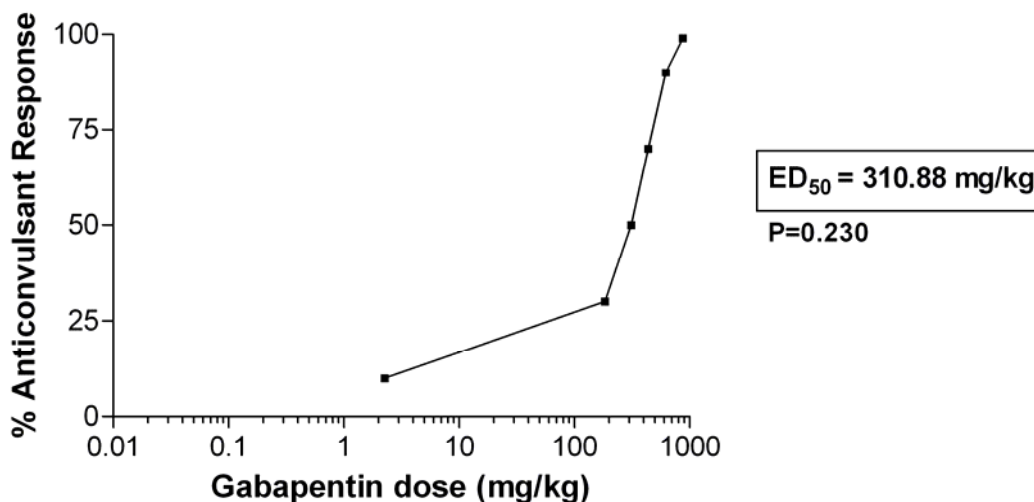


Figure 3. Anticonvulsant dose-effect curve, plotted from the result of the probit calculations, for the ability of gabapentin to block the development of soman-induced seizures when given as a pretreatment 30 min before soman exposure.

In both the pretreatment and therapy experiments, gabapentin did provide some protection against the lethal effects of soman. However, the 24-hr survivors were in very poor physical shape, having lost on average 17% of their pre-exposure body weight overnight (Figure 4). Such weight loss is characteristic of animals that experience uncontrolled nerve agent-induced seizures (McDonough et al., 2000).

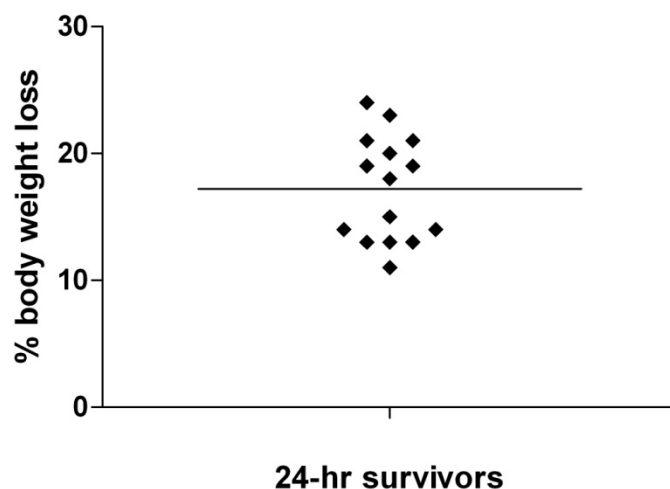


Figure 4. Percent weight loss of animals that were treated with gabapentin in both experiments and that survived 24 hr. Mean weight loss was 17.2% of baseline body weight.

Discussion

Gabapentin displayed no activity as an immediate anticonvulsant therapy for soman-induced seizures. However, gabapentin was capable of blocking the onset of soman-induced seizures when given as a pretreatment 30 min before agent challenge. This result is similar to the reports of Freitas et al. (2006) and Pereira et al. (2007), who showed that doses of 250 mg/kg gabapentin given as a pretreatment were able to reduce the number of animals that developed seizures subsequent to pilocarpine challenge. Based on the present results, it can be concluded that gabapentin is not capable of stopping nerve agent-induced seizures when the drug is administered therapeutically as would be the typical case in a military situation. Gabapentin did moderate the amplitude of the seizure activity when administered therapeutically, so it was not devoid of any effect. Whether higher doses would be of benefit under therapeutic conditions was not tested due to the very high cost of the compound (~\$400/50 mg). Higher doses could produce higher blood levels sooner and thus may be of some benefit under therapeutic conditions.

The results show that gabapentin does possess some anticonvulsant properties against nerve agent-induced seizures when administered as a pretreatment. Using a dose conversion recommended by the FDA to translate animal doses to human equivalent doses based on body surface area, the 310 mg/kg ED₅₀ dose effective as a pretreatment in guinea pigs translates to a pretreatment dose of 67.6 mg/kg gabapentin in humans, or >4700 mg for a 70-kg adult. This anticonvulsant pretreatment dose is substantially higher than the 900 – 1800 mg/day dose of gabapentin (divided into three smaller doses every 8 hr) recommended as adjunctive treatment of partial epilepsy or for the treatment of neuropathic pain. Patients taking gabapentin complain of dizziness, fatigue, somnolence, nausea and peripheral edema. A recent study using a prodrug formulation of gabapentin has shown that 50% of human volunteers that received up to 3125 mg equivalent doses of gabapentin experienced mild to moderate dizziness (Lal et al., 2009). Such side effects can significantly impair performance (Peterson, 2009), making gabapentin an impractical pretreatment option for use by the military where vigilance and the ability to take rapid coordinated action are essential. In a more general sense, the side effects of dizziness, fatigue and somnolence produced by gabapentin speak to the hypnotic and sedative actions of this drug. Such features are common to most classes of drugs (e.g., benzodiazepines, barbiturates) that have strong anticonvulsant actions controlling ongoing seizures in general (McNamara, 2006).

The actions of gabapentin were similar to those of fosphenytoin, another anticonvulsant drug previously tested using this model (McDonough et al., 2004). Fosphenytoin was highly effective as a pretreatment, most probably due to the very high blood levels achieved at the time of agent exposure. Given that gabapentin produced anticonvulsant effects only as a pretreatment and at very high doses, it is unlikely that this drug or similar compounds of this class (e.g., pregabalin, Lyrica[®]) would be considered as a replacement for, or a supplement to, diazepam or midazolam, which are highly effective at substantially lower doses in the treatment for nerve agent-induced seizures (McDonough et al., 1999, 2000, 2008; Shih et al., 2007).

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