

Serial-probe recognition in rhesus macaques: Effects of midazolam

Todd M. Myers*, Matthew G. Clark

Walter Reed Army Institute of Research, Division of Neurosciences, Silver Spring, MD, 20910-7500, USA

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Abstract

A serial-probe recognition task was used to assess the effects of midazolam on visual attention and short-term memory in three rhesus monkeys. On each trial, six unique alphanumeric sample stimuli (list items) were presented sequentially followed by a choice period. Choosing the ‘probe’ stimulus was correct if the probe matched one of the list items; otherwise, choosing the ‘default’ stimulus (a white square) was correct. Behavior was examined under a range of doses of midazolam (0.065, 0.13, 0.26, and 0.52 mg/kg IM). Midazolam did not significantly reduce choice accuracy or change the shape of the serial position function and did not significantly reduce choice responding. However, choice reaction time was significantly increased by the two highest doses of midazolam. Responding directed at the sample stimuli was reduced at the two highest doses of midazolam. Furthermore, 0.52 mg/kg midazolam significantly increased sample-stimulus reaction time at all six serial positions. Overall, these data suggest that the two highest doses of midazolam tested increase reaction time, but do not directly impair short-term visual recognition memory. This is noteworthy because such doses appear capable of protecting against nerve agent-induced seizures.

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1. Introduction

Benzodiazepines, such as diazepam and midazolam, are often prescribed for the treatment of anxiety and insomnia. This class of drugs is also used for sedation, muscle relaxation, analgesia, and amnesia pre-operatively in hospital settings. Another important capability of these drugs is in the treatment of active seizures (i.e., stopping ongoing seizure activity), whether the origin of the seizure is organic (e.g., epilepsy) or chemically induced (e.g., pesticide or chemical warfare nerve agent exposure). For example, in the clinical treatment of status epilepticus in adult humans, diazepam is usually administered intravenously (IV) as a bolus of 10–20 mg or rectally at 10–30 mg and these doses can be repeated, with the typical anticonvulsant dose being approximately 0.3–0.6 mg/kg. For

midazolam, a more potent compound, the dose range is 5–10 mg intramuscularly (IM), rectally, or IV and this dose can be repeated once after 15 min, with the typical anticonvulsant dose being approximately 0.15–0.30 mg/kg (Shorvon, 1994; Towne and DeLorenzo, 1999).

Rapid termination of chemically induced seizures is essential for preventing serious long-term neurological, behavioral, and cardiovascular deficits, thus the rapid onset of an anticonvulsant's effect is of critical importance (Castro et al., 1992; Lallement et al., 1999; McDonough et al., 1999; Murphy et al., 1993). Midazolam may offer several key advantages over diazepam in the rapid treatment of nerve agent-induced status epilepticus. Specifically, midazolam is much more water soluble than diazepam and is therefore more rapidly absorbed following IM injection (Gerecke, 1983). The ability to administer an anticonvulsant IM is also important because establishing venous access in actively convulsing patients is difficult, potentially delaying drug treatment and, thus, seizure termination (Fountain and Adams, 1999; Towne and DeLorenzo, 1999). Prompt administration of IM midazolam has been shown to stop seizures of various origins in both humans and nonhuman primates usually within 2–3 min and almost always within 10 min or less

* Corresponding author. Analytical Toxicology Division, Neurobehavioral Toxicology Branch, United States Army Medical Research Institute of Chemical Defense, 3100 Ricketts Point Road, Aberdeen Proving Ground, MD, 21010, USA. Tel.: +1 410 436 8380; fax: +1 410 436 8377.

E-mail address: todd.myers2@us.army.mil (T.M. Myers).

(Galdames et al., 1997; Hayward et al., 1990; Lahat et al., 1992; Mayhue, 1988; Wroblewski and Joseph, 1992).

The US military currently provides its forces with Convulsant Antidote for Nerve Agent (CANA) autoinjectors capable of delivering 10 mg of diazepam IM for use in a nerve agent exposure situation (equivalent to approximately 0.14 mg/kg for a 70-kg soldier). The CANA autoinjector is employed when a first responder needs to render aid (i.e., “buddy aid”) to incapacitated comrades exhibiting convulsions. Current doctrine states that medics and unit lifesavers can administer up to two additional doses at 10-min intervals to a convulsing casualty (Sidell, 1997), for a total of 30 mg of diazepam IM (equivalent to approximately 0.43 mg/kg for a 70-kg soldier). Given the necessity of IM administration in such circumstances and the apparent superiority of midazolam over diazepam in rate of absorption through this route, several studies have directly compared the efficacy of these two benzodiazepines in eliminating nerve agent-induced seizures. These studies, guided by current US military doctrine, administer pyridostigmine bromide pretreatment, then challenge animals with a large dose of nerve agent (e.g., 2LD50 of tabun, sarin, cyclosarin, soman, or VX), followed within minutes by IM injections of atropine and pralidoxime chloride (2-PAM). One of several benzodiazepine test compounds is administered at a specified time following the onset of seizure activity (as evidenced by cortical EEG electrodes) to gauge its anticonvulsant effect.

Using the approach outlined, McDonough et al. (1999) administered either IM diazepam or midazolam to guinea pigs 5 or 40 min after nerve agent-induced seizure onset to compare efficacies. Midazolam was more potent and more capable of rapid seizure control than diazepam at both delays to treatment. Shih et al. (2003) extended these findings by using six different chemical warfare nerve agents (tabun, sarin, soman, cyclosarin, VR, and VX) at 2LD50 as well as a 5LD50 dose of soman to induce seizures, and found midazolam to be the more potent and rapidly acting benzodiazepine anticonvulsant overall.

Using similar procedures in rhesus monkeys, Hayward et al. (1990) found that diazepam and midazolam (each at 1 mg/kg IM), given immediately following atropine and 2-PAM injections, were equally effective in hastening recovery and return to consciousness and reducing convulsions and brain lesions in rhesus monkeys following soman exposure. More recently, McDonough et al. (2002) directly compared the anticonvulsant efficacy of midazolam and diazepam in rhesus monkeys following a 2LD50 soman challenge. They found that a midazolam dose of 0.13 mg/kg, given once upon seizure onset and again 10 min later (for a combined dose of 0.26 mg/kg IM), was capable of terminating nerve agent-induced seizures in a majority of subjects, usually within about 30 min. An IM bolus dose of 0.32 mg/kg midazolam was comparably effective. In contrast, diazepam (0.4 to 0.63 mg/kg IM) terminated seizures in proportionally fewer subjects and seizure termination typically occurred after 80 min. These results suggest that the current treatment regimen with diazepam may be insufficient to terminate nerve agent-induced seizures and that midazolam may offer more reliable and more rapid seizure control, even at relatively low doses (about 0.3 mg/kg IM).

Unfortunately, benzodiazepines are known to produce unwanted behavioral side effects, such as sedation and amnesia (Lister, 1985; O’Boyle, 1988; Zbinden and Randall, 1967). However, such effects are generally observed at doses higher than those required for seizure control. For example, Castro (1995) found that diazepam significantly reduced accuracy of serial-probe recognition (SPR) performance in rhesus monkeys at doses of 1.6 mg/kg IM and higher, whereas choice reaction time was increased only at the highest dose (3.2 mg/kg IM). Schulze et al. (1989) used a battery of behavioral tests to evaluate the acute effects of diazepam in rhesus monkeys at doses of 0.25–4.0 mg/kg IV. They found that diazepam generally reduced delayed match-to-sample accuracy at doses of 1.0 and 2.0 mg/kg but did not significantly reduce task completion or sample-stimulus response rate even at 4.0 mg/kg. Performances on a progressive-ratio schedule and a color-position discrimination task were unaffected at these same doses. In contrast, task completion, response rate, and accuracy were generally reduced on an incremental repeated-acquisition task, but a clear dose-dependent effect was not observed (i.e., the 4.0-mg/kg dose did not reduce accuracy whereas the 1.0- and 2.0-mg/kg doses did). Accuracy on a temporal response-differentiation task was reliably decreased at doses of 1.0 mg/kg and higher. Taken together, the results of Schulze et al. (1989) and Castro (1995) suggest that diazepam doses of approximately 1.0 mg/kg and higher may alter various aspects of neurobehavioral functioning with or without direct response suppression.

Additionally, Hudzik and Wenger (1993) utilized simultaneous and delayed match-to-sample procedures in squirrel monkeys to evaluate doses of diazepam ranging from 0.1–1.0 mg/kg IM. Accuracy on the delayed match-to-sample task was reduced significantly at 0.55 and 1.0 mg/kg whereas accuracy on the simultaneous match-to-sample task was reduced significantly only at 1.0 mg/kg. It is noteworthy that sample-stimulus response rate was reduced significantly at doses of 0.3 mg/kg and higher. Baron and Wenger (2001) used a fixed 3-s delayed match-to-sample procedure in squirrel monkeys and found that diazepam decreased sample-stimulus response rate at doses of 1.0 mg/kg IM and higher, but significantly decreased accuracy only at 1.8 mg/kg and higher. Although the results were quite comparable across both Wenger studies, the slightly higher doses required for disruption in the latter study may have been due to the shorter retention interval (3 s) or to the decreased pre-treatment interval (15 min versus 30 min in the earlier study).

The goal of the present study was to determine whether doses of midazolam capable of controlling nerve agent-induced seizures produce deficits in attention, memory, and reaction time in a SPR task, a task that has been used extensively to evaluate compounds of military significance in rhesus monkeys (Castro, 1995, 1997; Castro et al., 1992, 1994; Matzke et al., 1999; Myers et al., 2002).

2. Method

The experimental protocol was approved by the Animal Care and Use Committee at the Walter Reed Army Institute of

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