USAMRICD-TR-18-09

Dexmedetomidine Intoxication in Rats

Todd M. Myers
Noah A. Rauscher
Nathaniel C. Rice
Mark C. Moffett

September 2018

Approved for public release; distribution unlimited

US Army Medical Research Institute of Chemical Defense
8350 Ricketts Point Road
Aberdeen Proving Ground, MD 21010-5400

an element of the

US Army Medical Research and Materiel Command

DISPOSITION INSTRUCTIONS:

Destroy this report when no longer needed. Do not return to the originator.

DISCLAIMERS:

The views expressed in this technical report are those of the author(s) and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government.

The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.

The use of trade names does not constitute an official endorsement or approval of the use of such commercial hardware or software. This document may not be cited for purposes of advertisement.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
18 September 2018	Technical Report	19 October 2016 to 20 July 2017

4. TITLE AND SUBTITLE
Dexmedetomidine Intoxication in Rats

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Myers, TM, Rauscher, NA, Rice, NC, Moffett, MC

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

US Army Medical Research Institute of Chemical Defense
ATTN: MCMR-CDR-ET
8350 Ricketts Point Road
Aberdeen Proving Ground, MD 21010-5400

8. PERFORMING ORGANIZATION REPORT NUMBER

USAMRICD-TR-18-09

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

National Institutes of Health
6610 Rockledge Drive
Bethesda, MD 20892

10. SPONSOR/MONITOR'S ACRONYM(S)

NIH

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This report provides preliminary information on overt toxicity observed following intraperitoneal injection of dexmedetomidine in rats. The dexmedetomidine doses (0.25, 0.5, and 1.0 mg/kg) were selected based upon their presumed ability to produce a robust response but not lethality. All doses produced immobilization within 5 minutes, and long-lasting intoxication was observed by reduced overnight food consumption and weight change. Behavioral performance, as indexed by the acquisition of a two-way discriminated active shuttle avoidance response 24 hours after dexmedetomidine injection, revealed no substantial differences from the control group, suggesting complete to near complete functional recovery by this time. These data and their conclusions are limited by the small number of subjects, limited ranges of doses, and inclusion of only one exposure route. Nevertheless, this study provides important preliminary information on the rapid onset and prolonged duration of intoxication that can be achieved by dexmedetomidine in a rat model. Utilizing this same animal model, more prompt and comprehensive operant behavioral testing following dexmedetomidine exposure appears warranted. Such an approach will further elaborate the time course and degree of toxicity and establish the foundation for behavioral studies of countermeasure efficacy.

15. SUBJECT TERMS

dexmedetomidine toxicity, immobilization, behavioral assessment, food consumption, rat

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Todd M. Myers
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UNLIMITED	17	**19b. TELEPHONE NUMBER** *(include area code)* 410-436-8380

ABSTRACT

This report provides preliminary information on overt toxicity observed following intraperitoneal injection of dexmedetomidine in rats. The dexmedetomidine doses (0.25, 0.5, and 1.0 mg/kg) were selected based upon their presumed ability to produce a robust response but not lethality. All doses produced immobilization within 5 minutes, and long-lasting intoxication was observed by reduced overnight food consumption and weight change. Behavioral performance, as indexed by the acquisition of a two-way discriminated active shuttle avoidance response 24 hours after dexmedetomidine injection, revealed no substantial differences from the control group, suggesting complete to near complete functional recovery by this time. These data and their conclusions are limited by the small number of subjects, limited ranges of doses, and inclusion of only one exposure route. Nevertheless, this study provides important preliminary information on the rapid onset and prolonged duration of intoxication that can be achieved by dexmedetomidine in a rat model. Utilizing this same animal model, more prompt and comprehensive operant behavioral testing following dexmedetomidine exposure appears warranted. Such an approach will further elaborate the time course and degree of toxicity and establish the foundation for behavioral studies of countermeasure efficacy.

INTRODUCTION

Dexmedetomidine (DEX) is the active (d) isomer of the adrenergic drug medetomidine, and is a potent and highly selective α2 adrenergic agonist. Its use was limited to veterinary sedation and anesthesia prior to FDA approval for human use in 1999. Since then it has been used and studied extensively in humans for a variety of clinical uses and disorders, often with great effect. While primarily used as a pre- or post-operative sedative or anesthetic adjunct, a search of the clinical literature shows its successful use in disorders such as alcohol, benzodiazepine, baclofen and opiate withdrawals, anticholinergic syndrome, and tachyarrhythmia, as well as an adjunct analgesic [1-9]. In high enough doses, it appears to be effective as a sole surgical anesthetic, producing a deep and sustained plane of anesthesia [10]. In animal studies, DEX can function as a neuroprotectant in traumatic, convulsive, and ischemic brain injuries and as an effective adjunct drug treatment for the cessation of drug-refractory status epilepticus in multiple animal models [11-16]. It has a wide dose range for various clinical uses and has a high index of safety, with doses far exceeding FDA dosing guidelines (> 10 fold) having been administered during anesthesia with no noted adverse effects [17]. DEX also has the benefit of being rapidly and fully reversible by another drug, atipamezole, an α2 adrenergic antagonist. When atipamezole is administered at a 60:1 ratio to DEX, it rapidly reverses the sedative and cardiovascular effects of the drug [18]. Remarkably, DEX can be administered intravenously (IV), intramuscularly (IM), orally (PO), and intranasally (IN), as well as by both the buccal and transdermal routes [19, 20]. It is typically administered IV as a 1.0 µg/kg loading dose followed by a continuous infusion in the dose range of 0.2 – 1.0 µg/kg/hr depending on the clinical application and the amount of sedation or anesthesia required, but doses as high as 10 µg/kg/hr have been reported with no adverse effects [10].

DEX exerts its central nervous system (CNS) effects by binding to all three subtypes of the α2 adrenergic receptors. By binding to the pre-synaptic α2 adrenergic receptor, DEX blocks binding of norepinephrine at the same site, interrupting a negative feedback loop which regulates norepinephrine release. Agonism at this site effectively mimics an excess of norepinephrine, reducing synaptic firing which greatly reduces presynaptic norepinephrine release and the resultant excitation of the postsynaptic tissue. In the case of DEX, its CNS effects are largely due to its agonism of α2 adrenergic receptors in the medial dorsal pons, namely, the locus ceruleus. The ascending noradrenergic pathway extending from the locus ceruleus, chiefly the ventrolateral preoptic nucleus and tuberomamillary nucleus, is similarly depressed by DEX due to downstream effects of decreased norepinephrine levels. This results in a release of γ-aminobutyric acid (GABA) and galanin as well as a decrease in histamine [21]. DEX also has an inhibitory effect on smooth muscle through the same adrenergic mechanism via the α2B receptor subtype. The effects of an IV dose of DEX (by far the most common clinical route of administration), which may be administered as a loading dose pushed over a 10-minute period, are anxiolysis and general sedation followed by sleep or unconsciousness and anesthesia at high doses. Following administration, there is an initial rise in blood pressure and heart rate, typically lasting no longer than 15 minutes, followed by a mild decrease in mean arterial pressure and heart rate which is maintained throughout the infusion. One of the most ideal clinical characteristics of the drug is that it does not

affect respiratory drive and does not compromise the airway. Due to its high lipophilicity, DEX conforms to a 2-compartment model of distribution and elimination. Its elimination half-life is around 2 hours, whereas its distribution half-life is 6 minutes, leading to a rapid onset and a short duration of action. Due to its wide distribution, clearance is also dependent upon the length of infusion, with prolonged infusions leading to large increases in elimination half-life. DEX is primarily excreted through the urine with a small portion excreted in the feces [22].

Data regarding the behaviorally intoxicating effects of DEX *when given alone* are still in need of experimental elaboration in multiple animal models. The preliminary data described and presented herein were collected during a study to screen anticonvulsant drugs for efficacy in treating the toxic effects of a $GABA_A$ antagonist chemical, tetramethylenedisulfotetramine (TETS). Because of the success by other labs in using DEX to treat drug-refractory seizures [11, 12], which is a common effect of TETS toxicity, it was included in the drug screen. As the present study involved gathering safety data (rats not exposed to TETS) on all of the drugs and doses administered, we were able to use that data to develop preliminary behavioral and toxicity data sets regarding three doses of DEX administered intraperitoneally (IP) in rats. Video recordings of all of the exposures and drug administrations allowed us to closely scrutinize and record the effects of the three DEX doses, including onset, length, and severity of intoxication immediately and for 5 hours after administration. Twenty-four hours after drug administration, rats were weighed and assessed for any overt signs of toxicity and then behaviorally assessed using a common learning task (active avoidance) prior to euthanasia at 25 hours postexposure.

METHODS

The broader context for this study was the evaluation of DEX as a potential treatment for tetramethylenedisulfotetramine (TETS) poisoning utilizing an established voluntary ingestion model [23]. The subjects reported upon herein comprised the “DEX safety” group, receiving no TETS poisoning. When appropriate, these rats were compared to saline vehicle injection control rats that also did not receive TETS but were in all other ways treated similarly.

Subjects

Male Sprague-Dawley rats were obtained from Charles River (SAS SD 400; Wilmington, MA) and housed individually to accomplish controlled access to food. Animals were kept on a 12 h light/dark cycle, and all experiments were conducted during the light phase. Food regulation was employed to increase the likelihood of rapid consumption of a small piece of food (Froot Loops®; Kellogg Company, Battle Creek, MI) and to ensure an empty stomach during oral TETS exposure. A measured portion of rat chow was provided daily in each afternoon to maintain the subjects at approximately 90% of the free-feeding weights determined from growth-curves. The rats weighed between 269.1 to 328.2 g at the time of exposure (average 289 g). Water was available ad libitum in the rats' home cages.

The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense (USAMRICD), and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. The USAMRICD is a research facility fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Apparatus and Procedure

Froot Loops (180–220 mg) had 85-95 ul of acetone (>99.5% purchased from Sigma Aldrich, St. Louis, MO) applied approximately 1 hour prior to presentation and consumption, allowing for full evaporation in a certified fume hood. In an observation cage (standard rodent cage measuring 15 cm L × 7 cm W × 8 cm H) with Alpha-Dri bedding (Shepherd Specialty Papers, Watertown, TN), each rat was given a single Froot Loop and observed until the cereal morsel was completely consumed. DEX (Dexdomitor©, 0.5 mg/ml, Zoetis, Parsippany, NJ) was administered via intraperitoneal (IP) injection 10 minutes following TETS poisoning. DEX was diluted in normal saline to a concentration of 0.25 mg/ml for the lowest dose. Volumes of injection were 1 ml/kg for the 0.25 and 0.5 mg/kg doses and 2 ml/kg for the 1.0 mg/kg dose. All injections were given IP using a 1 ml syringe with a 5/8-inch 25 gauge needle.

Overt Toxicity Assessment

Rats were monitored continuously for at least 10 minutes prior to and 5 hours following drug administration via continuous video recording using two (front and side angle) high-resolution color cameras per subject and a CCTV system. Any overt toxic signs or abnormal behaviors during this period were noted. At 24 hours after drug administration, food wastage and body weights were recorded. The rats were also assessed for toxic signs at 24 hours, before beginning the shuttlebox avoidance assessment.

Shuttlebox Avoidance

Twenty-four hours after agent exposure, animals were assessed for learning in a two-way active discriminated shuttlebox avoidance task. The shuttlebox avoidance assessment was conducted in GEMINI test chambers (San Diego Instruments Inc., San Diego, CA) using custom-written software. The avoidance session began with a 5-minute acclimation period during which all chamber illumination was off. In each test session, 50 discrete trials were presented. At the start of each trial, the photobeam array detected the location of the rat and presented the warning stimulus (WS; a light and 75 (±2) db tone) in that compartment. Failure to ambulate to the darkened compartment within 5 s resulted in a 1.2 mA scrambled shock applied to the grid floor while the WS continued. Ambulating into the darkened compartment within 15 s terminated all stimuli (WS, shock) and was registered as an escape response. Failure of the animal to ambulate at all within the 15 s maximal shock duration was recorded as a failed escape or “no response.” Shock could be avoided on all trials by promptly ambulating (within 5 s) into the dark compartment after onset of the WS (and, thus, prior to shock). Trials were separated by a pseudorandom inter-trial interval (20 ± 5 s). Dependent measures included number of avoidance responses, number of escape

responses, and their respective latencies, as well as inter-trial crossings and response failures (none of which occurred). Only avoidance responses are presented herein.

Euthanasia

Immediately following completion of the shuttlebox avoidance test, rats were euthanized with an overdose of a pentobarbital-based solution administered IP.

Subject Allocation

Three experimental animals were included in the lowest and highest dose groups for DEX (0.25 and 1.0 mg/kg); four rats were included at the medium dose group (0.5 mg/kg) and were compared to corresponding values for five saline vehicle control animals to properly contextualize food consumption, body weight changes, and shuttlebox avoidance performance. The vehicle control group received saline in an equivalent volume to those in the DEX groups.

Data Analysis

Inferential statistical analyses were not warranted based upon the small number of subjects and the limited range of doses. Nevertheless, data were orderly enough to discern general effects of these DEX doses and dose-dependent trends in most measures. Descriptive (non-inferential) statistics (means and ranges) are reported below to provide a description of experimental outcomes, trends, and inter-subject variability.

RESULTS

Figure 1 shows the latency between administration of DEX and the onset of complete immobilization, defined as sustained absence of movement (except breathing) for over one full hour. The onset of immobilization was rapid, averaging 218 (range 200-252) seconds at the lowest dose (0.25 mg/kg) and averaging only 82 (range 42-144) seconds at the highest dose (1.0 mg/kg). The intermediate dose produced a mean immobilization latency of 312.3 (range 99-819) seconds. The lack of clear monotonic dose-dependency is due to a higher-than-expected mean at the intermediate dose which was due to one rat that exhibited profound ataxic movements (rather than complete immobilization) during the first 13.65 minutes (819 seconds) after DEX administration before becoming completely immobile. Thus, at these doses, the clear majority of rats (9 of 10) exhibited complete and sustained immobilization within 4.2 minutes.

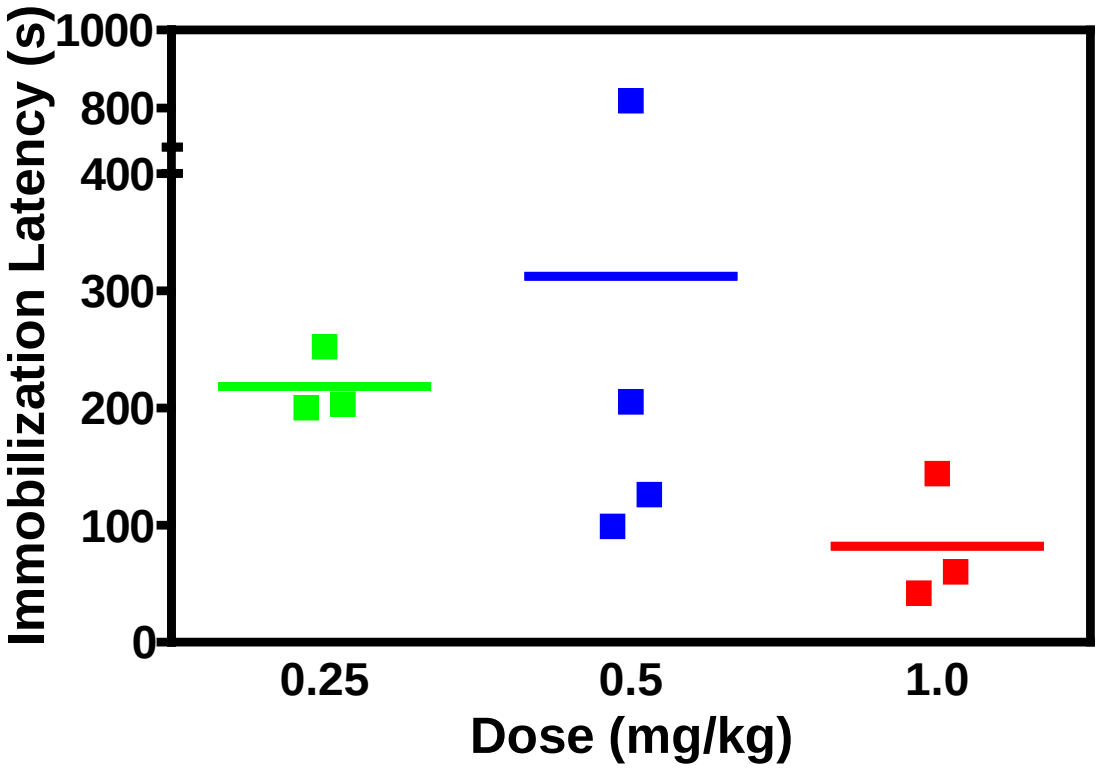

Figure 1. Immobilization latency (in seconds) as a function of DEX dose. Symbols represent the response of individual rats and the solid lines represent the group mean.

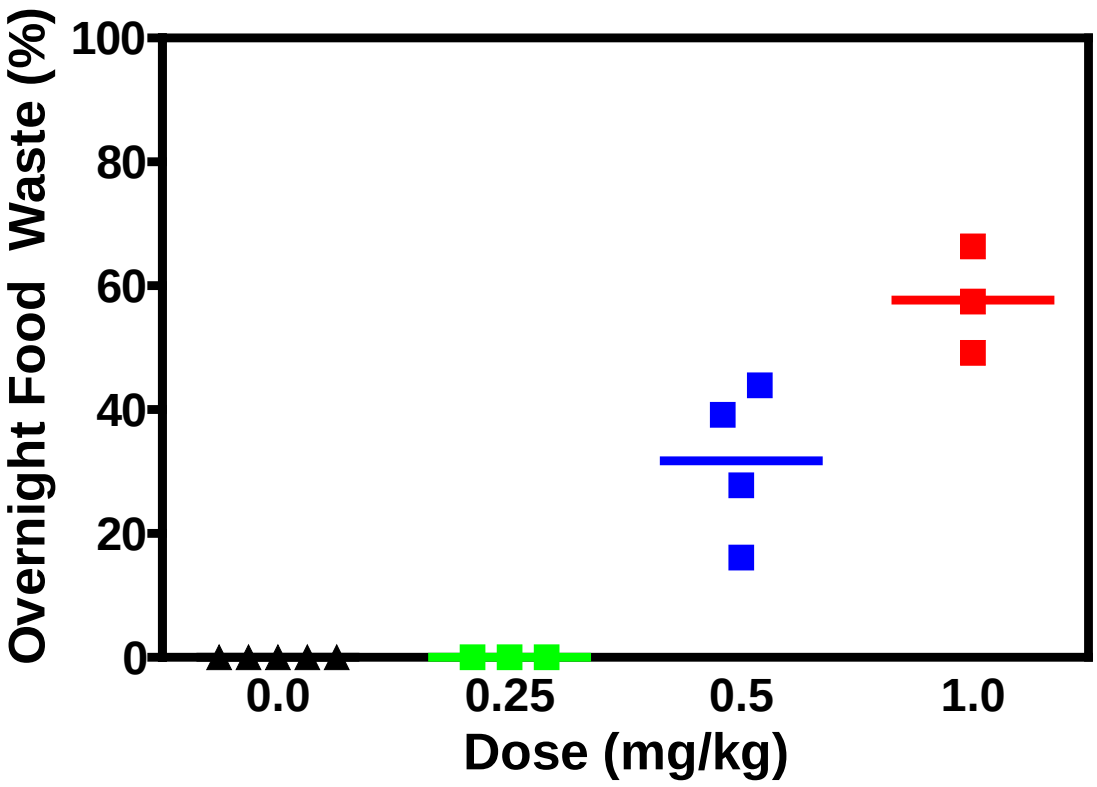

Figure 2. Percent overnight food wastage as a function of DEX dose. Saline control rats are shown in the 0.0 mg/kg dose group. Symbols represent the response of individual rats and the solid lines represent the group mean.

Figure 2 shows overnight food wastage for each DEX dose group as a percentage of the amount provided. The saline vehicle control data are also shown (indicated as the 0.0 mg/kg dose group). In the saline control group and at the lowest DEX dose, no food was wasted (means and ranges equaled 0). At the intermediate and highest doses, food wastage averaged 28% (16.13-43.94%) and 58% (49.19- 66.38%), respectively. Thus, a dose-dependent trend in food wastage was observed.

Figure 3 shows the 24-hour change in body weight following DEX exposure as percentage of each individual's pre-exposure weight. Under saline control, average normal weight gain of approximately 5% (1.0-8.0%) was observed. At the lowest DEX dose, a somewhat comparable but slightly lower mean weight gain of 3.06% (1.97-4.97%) was observed. At the intermediate dose, an average weight change of -0.42% (-1.81-1.0%) was observed, suggesting a disruption of normal weight gain. At the highest DEX dose of 1.0 mg/kg, a sizable weight change of -3.46% (-5.54-0.11%) was observed. This loss in body weight was well outside the expected gain and likely resulted from high-dose DEX administration.

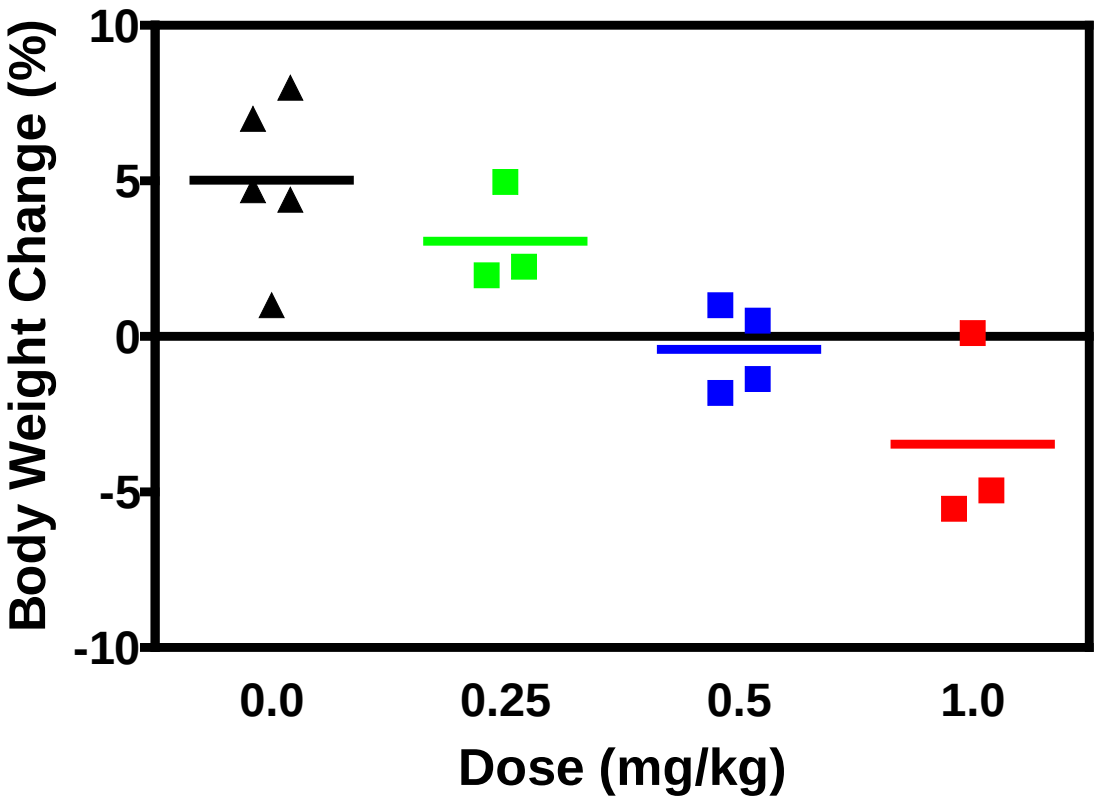

Figure 3. Percent overnight body weight change as a function of DEX dose. Saline control rats are shown in the 0.0 mg/kg dose group. Symbols represent the response of individual rats and the solid lines represent the group mean.

Figure 4 shows the primary dependent measure from the acquisition of shuttlebox avoidance performance 24 hours after DEX injection. Overt signs of DEX toxicity were absent 24 hours after DEX injection, and avoidance performance was not severely affected. The percentage of avoidance responses under saline vehicle conditions (mean 77.2%; range 68-92%) approximated the 0.25 mg/kg DEX dose (mean 80%; range 52-100%), indicating no lingering performance impairment as a result of DEX exposure. Likewise, at the higher DEX doses of 0.5 (mean 61.5%; range 32-86%) and 1.0 mg/kg (mean 56.7%; range 38-68%), the percentage of avoidance responses was fairly high, suggesting only a slight decrement in avoidance acquisition (if any).

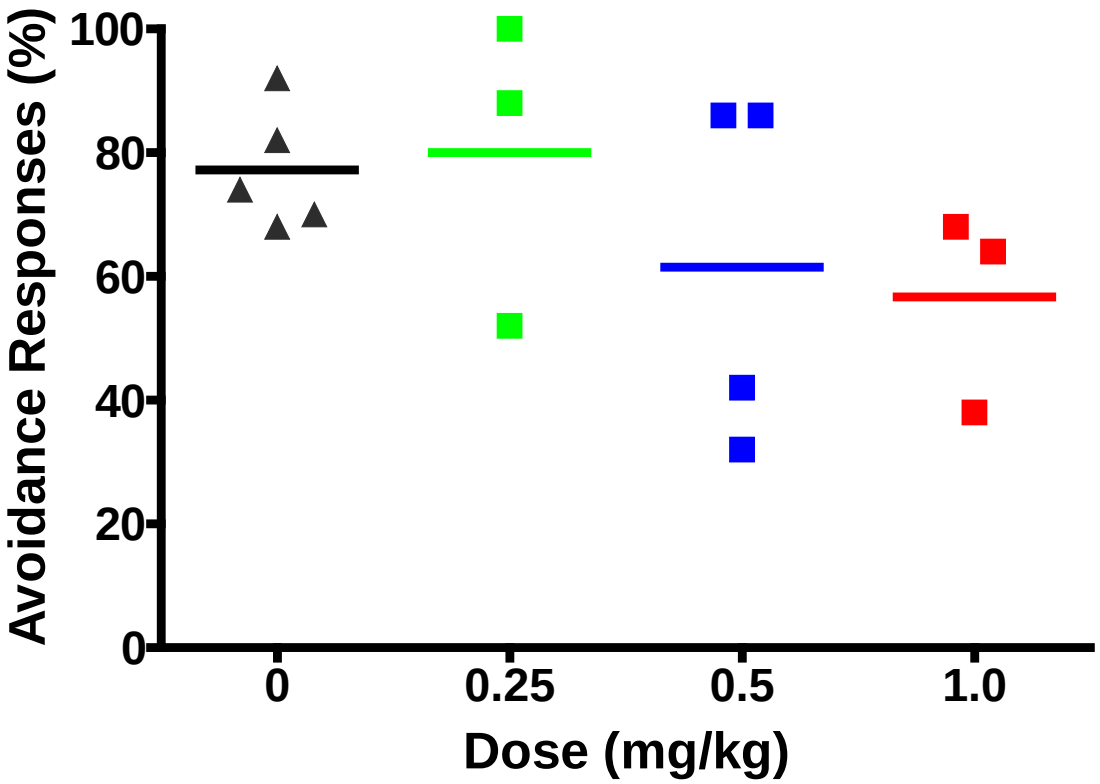

Figure 4. Percent avoidance responses as a function of DEX dose. Saline control rats are shown in the 0.0 mg/kg dose group. Symbols represent the response of individual rats and the solid lines represent the group mean.

DISCUSSION

The present report summarizes experimental data regarding the onset and duration of DEX toxicity in rats following IP injection. At doses ranging from 0.25 to 1.0 mg/kg IP, rats rapidly exhibited profound ataxia followed by immobilization (the complete absence of movement except breathing). Measurements of overnight food consumption and body weight changes suggested a dose-dependent time to functional recovery. Indeed, the most obvious untoward DEX side effects at 24 hours were food wastage and resultant mild weight loss. Both measures appeared to be dose dependent, and likely resulted from prolonged intoxication and differential recovery times. Other possible causes are reduced caloric need due to prolonged inactivity or a DEX-induced inappetence. A well-validated behavioral test (shuttlebox avoidance based upon aversive stimulation) demonstrated that functional recovery was largely complete 24 hours after DEX exposure.

Although these data were acquired in the context of a larger study evaluating the toxicity of TETS and the safety of DEX as a medical countermeasure, the information obtained is useful for understanding DEX toxicity and establishing a range of doses for evaluation in more comprehensive, subsequent studies of DEX intoxication. Specifically, we now know that the onset and duration of ataxia and immobilization following IP DEX administration is rapid and prolonged in this rat strain at the doses studied, and relatively invariant across subjects. More extensive dose evaluations, possibly in other rat strains, will provide systematic replication and extension of these findings. Moreover, behavioral evaluation to quantitatively characterize onset, degree, and duration of intoxication and the time course and completeness of functional recovery is warranted.

The DEX doses presented in this report overlapped and exceeded those commonly used surgically (i.e., 0.25-0.5 mg/kg, when mixed with ketamine). Additionally, the dose-dependent onset and duration of immobilization across our dose range of 0.25-1.0 mg/kg suggest the possibility that even more rapid and prolonged immobilization may be achieved at higher doses. A similar study conducted in rats found that doses of DEX up to 3 mg/kg IP produced a dose-dependent hypnotic response (as defined by loss of righting reflex). The same study found that doses in excess of 3 mg/kg did not increase the duration of DEX's hypnotic action and that very high doses (10 mg/kg IP) produced lethality in >50% of the rats [24]. A veterinary safety study conducted by the European Medicines Agency found that the "maximum non-lethal dose" of DEX in rats was 1-5 mg/kg subcutaneously (SC) and that the only toxic sign observed following a single dose of DEX was corneal opacity [25]. Apart from one rat in the present study with possible mild hematuria the day following administration of 1.0 mg/kg DEX, no suggestion of untoward anatomical toxicity was observed. Thus, higher DEX doses (~3-5 mg/kg IP or SC) may produce more rapid, profound, and prolonged intoxication without producing lethality, based on both human safety data [17] and rat studies described above.

In these studies, as well as our study, onset of intoxication and sedation (by their measures as well as ours) were rapid and reliable following IP, IV or SC administration. Further experiments should be conducted to better determine the full range of doses at

which DEX is both safe and effective in various species through various routes of administration. Further, experiments that aim to better detect and characterize any potential toxic effects caused by ultra-high DEX doses should be carried out in multiple species. Highly sensitive behavioral measures may be ideal for detecting subtle toxic effects of high-dose DEX in both the short- and long-term studies. Such experiments carried out by our group in the past have successfully characterized the onset, length, and severity of toxic effects of other chemical toxicants using an operant-behavioral model [23, 26]. This model is easily replicable and adapted to other drugs or toxicants, which makes it an ideal choice for characterizing any toxic neurobehavioral effects of high-dose DEX with a high degree of sensitivity. Likewise, comparable behavioral methods are available for assessing drug toxicity in non-human primates and were recently successful not only in characterizing carfentanil toxicity, but also at demonstrating the safety, efficacy, and duration of action of varying doses of medical countermeasure treatment [27]. Although DEX appears to have a relatively large margin of safety in both humans and animals, such neurobehavioral studies should be carried out to ensure that high doses do not cause more nuanced cognitive/behavioral deficits or long-term neurological sequelae which more directly reflect relevant dimensions of concern and almost certainly would not be apparent via gross pathological examination.

REFERENCES

[1] Chrysostomou, C., Beerman, L., Shiderly, D., Berry, D., Morell, V. O., Munoz, R. Dexmedetomidine: a novel drug for the treatment of atrial and junctional tachyarrhythmias during the perioperative period for congenital cardiac surgery: a preliminary study. Anesthesia & Analgesia. 2008,107:1514-22.

[2] Darrouj, J., Puri, N., Prince, E., Lomonaco, A., Spevetz, A., Gerber, D. R. Dexmedetomidine infusion as adjunctive therapy to benzodiazepines for acute alcohol withdrawal. Annals of Pharmacotherapy. 2008,42:1703-5.

[3] Maccioli, G. A. Dexmedetomidine to facilitate drug withdrawal. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2003,98:575-7.

[4] Morr, S., Heard, C. M., Li, V., Reynolds, R. M. Dexmedetomidine for acute baclofen withdrawal. Neurocrit Care. 2015,22:288-92.

[5] Mueller, S. W., Preslaski, C. R., Kiser, T. H., Fish, D. N., Lavelle, J. C., Malkoski, S. P., et al. A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Critical Care Medicine. 2014,42:1131-9.

[6] Multz, A. S. Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. Anesthesia & Analgesia. 2003,96:1054-5.

[7] Oschman, A., McCabe, T., Kuhn, R. J. Dexmedetomidine for opioid and benzodiazepine withdrawal in pediatric patients. American Journal of Health-System Pharmacy. 2011,68:1233-8.

[8] Rayner, S. G., Weinert, C. R., Peng, H., Jepsen, S., Broccard, A. F. Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. Annals of Intensive Care. 2012,2:12.

[9] Walker, A., Delle Donne, A., Douglas, E., Spicer, K., Pluim, T. Novel use of dexmedetomidine for the treatment of anticholinergic toxidrome. J Med Toxicol. 2014,10:406-10.

[10] Ramsay, M. A., Luterman, D. L. Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2004,101:787-90.

[11] Kan, M. C., Wang, W. P., Yao, G. D., Li, J. T., Xie, T., Wang, W., et al. Anticonvulsant effect of dexmedetomidine in a rat model of self-sustaining status epilepticus with prolonged amygdala stimulation. Neurosci Lett. 2013,543:17-21.

[12] McCarren, H. S., Arbutus, J. A., Ardinger, C., Dunn, E. N., Jackson, C. E., McDonough, J. H. Dexmedetomidine stops benzodiazepine-refractory nerve agent-induced status epilepticus. Epilepsy Research. 2018,141:1-12.

[13] Cosar, M., Eser, O., Fidan, H., Sahin, O., Buyukbas, S., Ela, Y., et al. The neuroprotective effect of dexmedetomidine in the hippocampus of rabbits after subarachnoid hemorrhage. Surgical Neurology. 2009,71:54-9.

[14] Halonen, T., Kotti, T., Tuunanen, J., Toppinen, A., Miettinen, R., Riekkinen, P. J. Alpha 2-adrenoceptor agonist, dexmedetomidine, protects against kainic acid-induced convulsions and neuronal damage. Brain Res. 1995,693:217-24.

[15] Jolkkonen, J., Puurunen, K., Koistinaho, J., Kauppinen, R., Haapalinna, A., Nieminen, L., et al. Neuroprotection by the alpha2-adrenoceptor agonist, dexmedetomidine, in rat focal cerebral ischemia. Eur J Pharmacol. 1999,372:31-6.

[16] Ma, D., Hossain, M., Rajakumaraswamy, N., Arshad, M., Sanders, R. D., Franks, N. P., et al. Dexmedetomidine produces its neuroprotective effect via the alpha 2A-adrenoceptor subtype. Eur J Pharmacol. 2004,502:87-97.

[17] Wagner, D. S., Brummett, C. M. Dexmedetomidine: as safe as safe can be. In Seminars in Anesthesia, Perioperative Medicine and Pain: Elsevier; 2006. p. 77-83.

[18] Scheinin, H., Aantaa, R., Anttila, M., Hakola, P., Helminen, A., Karhuvaara, S. Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific α2-adrenoceptor antagonist atipamezolea pharmacodynamic and kinetic study in healthy volunteers. The Journal of the American Society of Anesthesiologists. 1998,89:574-84.

[19] Anttila, M., Penttilä, J., Helminen, A., Vuorilehto, L., Scheinin, H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. British Journal of clinical Pharmacology. 2003,56:691-3.

[20] Kivistö, K. T., Kallio, A., Neuvonen, P. J. Pharmacokinetics and pharmacodynamics of transdermal dexmedetomidine. European Journal of clinical Pharmacology. 1994,46:345-9.

[21] Nelson, L. E., Lu, J., Guo, T., Saper, C. B., Franks, N. P., Maze, M. The α2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2003,98:428-36.

[22] Giovannitti Jr, J. A., Thoms, S. M., Crawford, J. J. Alpha-2 adrenergic receptor agonists: a review of current clinical applications (Dexmedetomidine). Anesthesia Progress. 2015,62:31-8.

[23] Rice, N. C., Rauscher, N. A., Langston, J. L., Myers, T. M. Behavioral intoxication following voluntary oral ingestion of tetramethylenedisulfotetramine: dose-dependent onset, severity, survival, and recovery. Neurotoxicology. 2017,63:21-32.

[24] Doze, V. A., Chen, B.-X., Maze, M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central alpha-2 adrenoceptors. Anesthesiology. 1989,71:75-9.

[25] EuropeanMedicinesAgency. CVMP/772/02 - Dexmedetomidine Evaluation. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/veterinary/000070/WC500062496.pdf2002.

[26] Rice, N. C., Rauscher, N. A., Langston, J. L., Myers, T. M. Behavioral toxicity of sodium cyanide following oral ingestion in rats: Dose-dependent onset, severity, survival, and recovery. Food and Chemical Toxicology. 2018.

[27] Langston, Jeffrey L., Moffett, Mark C., Makar, Jennifer R., Burgan, Bradley M., Myers, Todd M. Carfentanil toxicity in the African green monkey: therapeutic efficacy of naloxone. USAMRICD-TR-18-03. U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD, August 2018. AD1057869