The Journal of Emergency Medicine, Vol. 48, No. 3, pp. 313–324, 2015
Published by Elsevier Inc.
Printed in the USA
0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2014.06.047

Pharmacology in Emergency Medicine

COMPARISON OF THE EFFECTS OF KETAMINE AND MORPHINE ON PERFORMANCE OF REPRESENTATIVE MILITARY TASKS

Steven J. Gaydos, MD, MPH, Amanda M. Kelley, MA, PHD, Catherine M. Grandizio, BA, MS, Jeremy R. Athy, BA, MA, and P. Lynne Walters, MB CHB

U.S. Army Aeromedical Research Laboratory, Fort Rucker, Alabama
Corresponding Address: Steven J. Gaydos, MD, MPH, U.S. Army Aeromedical Research Laboratory, Warfighter Performance and Health Division, 6901 Farrell Road, Fort Rucker, AL 36362

☐ **Abstract—Background: When providing care under combat or hostile conditions, it may be necessary for a casualty to remain engaged in military tasks after being wounded. Prehospital care under other remote, austere conditions may be similar, whereby an individual may be forced to continue purposeful actions despite traumatic injury. Given the adverse side-effect profile of intramuscular (i.m.) morphine, alternative analgesics and routes of administration are of interest. Ketamine may be of value in this capacity. Objectives: To delineate performance decrements in basic soldier tasks comparing the effects of the standard battlefield analgesic (10 mg i.m. morphine) with 25 mg i.m. ketamine. Methods: Representative military skills and risk propensity were tested in 48 healthy volunteers without pain stimuli in a double-blind, placebo-controlled, crossover design. Results: Overall, participants reported more symptoms associated with ketamine vs. morphine and placebo, chiefly dizziness, poor concentration, and feelings of happiness. Performance decrements on ketamine, when present, manifested as slower performance times rather than procedural errors. Conclusions: Participants were more symptomatic with ketamine, yet the soldier skills were largely resistant to performance decrements, suggesting that a trained task skill (autonomous phase) remains somewhat resilient to the drugged state at this dosage. The performance decrements with ketamine may represent the subjects' adoption of a cautious posture, as suggested by risk propensity testing whereby the subject is aware of impairment, trading speed for preservation of task accuracy. These results will help to inform the casualty care community regarding appropriate use of ketamine as an alternative or opioid-sparing battlefield analgesic. Published by Elsevier Inc.**

☐ **Keywords—prehospital care; military medicine; soldier skills**

INTRODUCTION

Tragically, to varying degrees, casualties are virtually inevitable in sustained combat operations. Although lamentable in their own right, casualties can also jeopardize mission completion, reduce combat effectiveness, and increase exposure and danger to others. To this end, the goals of Tactical Combat Casualty Care (TCCC) include treating the casualty, preventing additional casualties, and completing the mission (1). In some instances, the best initial "medicine" during care under fire may dictate that the casualty take cover or remain engaged in other military tasks. Indeed, the extent to which a casualty can remain capable and engaged may prove critical for care under fire, self-evacuation, and safety and effectiveness of the unit. It is with ease that one can make the

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Received: 7 February 2014; Final submission received: 15 April 2014;
Accepted: 30 June 2014

intellectual transition to similarities with prehospital care in other austere environments such as wilderness or expedition medicine. In such cases, treatments and biologics are often limited, and the patient or team member may have to continue on for a period of time with purposeful tasks despite traumatic injury.

Timely and effective analgesia is essential in trauma casualty care. The types of injuries encountered on the modern battlefield resulting from high-energy blast or direct-fire weapons are significant and can cause tremendous pain. It is not suggested or recommended that casualties sustaining significant trauma continue mission-oriented tasks as a matter of convention. However, some situations are conceivable whereby the need is present due to extreme circumstance, there are no good alternatives, and evacuation is not imminent. Since its discovery in the early 19th century and subsequent well-documented military use in the Crimean War and American Civil War, morphine (and its derivatives) has remained the mainstay for acute severe battlefield pain (2). Its perpetuity in this capacity speaks to its strengths and desirable qualities as a potent analgesic. Indeed, the 10-mg intramuscular (i.m.) morphine injector has been the current battlefield standard for acute severe pain for some time. However, morphine can be associated with untoward side effects (including hypotension, sedation, nausea and vomiting, respiratory depression, euphoria/dysphoria, and others), and the military medical community has searched for adjuvants and alternatives to augment or spare morphine use in some instances (3,4).

Morphine can detract from a casualty's ability to "remain capable" on the battlefield if required by the situation, particularly at higher doses. One combat medic field reference, for example, states that the casualty should be considered nonambulatory after administration of morphine (5). TCCC mandates that combatants with altered mental status must be disarmed due to the risk of inappropriate weapon use (1). Furthermore, the commonly used i.m. route is notoriously problematic under conditions of hemorrhage, hypovolemia, and hypothermia whereby absorption is poor, analgesia is unreliable, and overdose remains a concern with subsequent volume resuscitation during later stages of care.

Although morphine is a very good analgesic, there remains interest in potential alternatives, adjuvants, and substitute routes of drug delivery for battlefield pain control. The guidance of "improved drugs to manage pain" is listed specifically as a key technology to be explored and developed as a Health Service Support Force Operating Capability (6). Likewise, pain control research remains a designated program area of the Army's Combat Casualty Care Research Program (CCCRP) with the mission of "fostering the development of biologics, pharmaceuticals, and medical devices that improve the first responder's capability to provide effective treatment more rapidly and as close to the place of the injury as possible" (7). Medics with direct combat experience have also requested improved battlefield analgesia—in particular, seeking alternatives to morphine and alternate routes of administration (Chief of Anesthesia, U.S. Army Institute of Surgical Research, personal communication).

In 2009, the Royal Centre for Defence Medicine (United Kingdom) conducted a study of clinical opinion assessing the effectiveness of current battlefield analgesia and options for improvement (8). Surveying 122 clinicians (emergency physicians and nurses, anesthesiologists, surgeons, intensivists, general practitioners, and combat medical technicians), more than half (52%) disagreed that i.m. morphine had the ideal analgesic properties for the military prehospital arena. The majority of respondents reported simplicity, reliability, and rapid onset of action as having the highest importance. Furthermore, a majority (70%) responded that an analgesic more potent and with a more rapid onset than morphine was desirable. Seventy-four percent reported that a nasal spray was an acceptable delivery method.

The concept of exploiting routes of drug administration other than i.m. is not new (9–11). These may include buccal transmucosal, intranasal aerosol, transdermal, and others (12). Early intravenous access with more precise titration is ideal, but certainly problematic under combat conditions (8,11). Morphine is an excellent, time-tested battlefield analgesic for acute severe pain, but does have some shortcomings. And the i.m. delivery route can be problematic, especially with shock states common with battlefield-type injuries. As part of larger programs to address these issues, this study was sponsored by the Army's CCCRP in support of an Integrated Product Team researching intranasal (i.n.) ketamine as a potential battlefield analgesic.

Although largely used as an anesthetic, use of ketamine as an analgesic is not surprising given the *N*-methyl-D-aspartate receptor's significant role in pain perception. Furthermore, it has been known for over 25 years that ketamine interacts with opioid receptors (13). Other purported receptor interactions include norepinephrine, serotonin, and muscarinic (14). Recommended analgesic dose ranges vary (0.4–1.0 mg/kg i.m. and 0.2–0.5 mg/kg i.v.) and are generally given as lower than that needed for anesthetic purposes (5–10 mg/kg i.m. or 1–2.5 mg/kg i.v.) (15,16). The efficacy and opioid-sparing effects of subanesthetic ketamine for analgesia have been studied previously, as well as experiences in combat and other prehospital care arenas (16–21).

Department of Defense involvement with an intranasal ketamine development effort began in approximately 2000. An analgesic product was envisioned that could provide acute pain relief while preserving the casualty's

ability to perform soldier tasks and retain functionality (22). Other desirable attributes included noninvasive delivery route, rapid onset and action, and opioid-sparing effects. The Walter Reed Army Institute of Research conducted preliminary testing in this effort, evaluating cognitive performance effects of four dosages of ketamine (30, 60, 90, and 120 ng/mL) over 120 min of continuous i.v. infusion (23). In short, ketamine impaired response times to visual stimuli, manual dexterity, ability to consolidate information, visual information processing accuracy, design organization accuracy, cognitive estimation, and increased perseverative errors. Ketamine increased self-ratings of dissociation, but did not impair retrograde memory.

The objective of the present study was to delineate performance decrements in basic military tasks by comparing the effects of the standard battlefield analgesic (10 mg i.m. morphine) with a ketamine dose of 25 mg i.m. Dosages were selected to compare the longstanding morphine standard with a potential new article for use at the point of injury. The 25-mg dose was representative of a potential i.n. product: two doses of 30 mg i.n. ketamine in a self-contained single-use spray device (60 mg at 40% i.n. bioavailability equates to approximately to 25 mg i.m.). A standard dose was selected for the test articles for the entire study population to simulate conditions whereby weight-based dosing is impractical at the point of injury. A secondary objective was to identify symptoms and events related to the administration of the analgesic levels of ketamine in a simulated training environment. For statistical purposes, we hypothesized that 25 mg of i.m. ketamine would produce fewer and less severe performance decrements on the representational military tasks in the test battery than 10 mg i.m. morphine.

MATERIALS AND METHODS

The study was approved in advance by U.S. Army Medical Research and Materiel Command Office of Research Protections Institutional Review Board. After extensive informational briefings, volunteers provided written informed consent prior to participation. An ombudsman was present for all informed consent sessions. Robust medical safeguards were emplaced under the direction of the study physicians, and an external medical monitor was assigned to the study.

Study Design

The study consisted of a double-blind, placebo-controlled, crossover Latin square design (study physicians were not blinded for safety reasons). Three arms included ketamine vs. morphine vs. placebo:

- 25 mg of ketamine (50 mg/mL); 0.5 mL i.m. (deltoid)
- 10 mg of morphine (25 mg/mL); 0.4 mL i.m. (deltoid)
- 0.9% sodium chloride (saline) solution; 0.5 mL i.m. (deltoid)

There were no induced pain stimuli to participants. Testing consisted of representative military tasks based on the *Soldier's Manual of Common Tasks* (24,25). Tasks and test metrics are presented in Table 1.

Participants

Data were collected on 48 participants; three participants were female. Ages ranged from 22 to 42 years. Subject body mass index ranged from 22.5 to 32.5 kg/m^2. Soldier

Table 1. Assessments and Presentation Details*

Assessment	Presentation Details
Engage Targets with an M16/M4 Series Rifle	Computerized simulation range
Shoot—Don't Shoot (Identify Friend/Foe/Neutral)	Computerized simulation range
Correct Malfunctions of an M16/M4 Series Rifle	Computerized simulation range
Protect Yourself from Chemical, Biological, Radiological, and Nuclear (CBRN) Injury or Contamination with Mission-Oriented Protective Posture (MOPP) Gear	Four subtasks in accordance with each MOPP level: 1 = don trousers/jacket; 2 = don overboots, 3 = don protective mask, and 4 = don protective gloves
Protect Yourself from Chemical and Biological (CB) Contamination Using Your Assigned Protective Mask (Promask)	Two subtasks: 1 = don/clearing/ check mask; 2 = secure hood
Perform Voice Communications	Scenario based with AN/PRC-90 handheld radio
Request Medical Evacuation (MEDEVAC)	Scenario based with map. Two subtasks: 1 = MEDEVAC lines 1–5; 2 = MEDEVAC lines 6–9
Evaluation of Risks (EVAR) Visual Analogue Scale	Self-administered questionnaire
Symptom Questionnaire	Technician-administered questionnaire
Vital Signs	Technician-administered

* Skill tasks were extracted from the *Soldier's Manual of Common Tasks, Skills Level 1* (Soldier Training Publication No. 21-1-SMCT, Department of the Army, 2006) and *Soldier's Manual of Common Tasks, Skills Level 2, 3, and 4* (Soldier Training Publication No. 21-24-SMCT, Department of the Army, 2008) (24,25).

ranks ranged from Sergeant (E-5) to Captain (O-3). Eight Military Occupational Specialties (MOS) were represented.

Procedure

Participant testing was completed over 7-day blocks. Within each week-long block, a maximum of three groups of four participants (12 per week) were scheduled. Participants presented with varying military backgrounds and experience levels with the solider skills. Day 1 (Saturday) was dedicated to familiarization with the performance tasks and testing procedures, followed by training to asymptote. Day 2 (Sunday) entailed baseline testing only. Testing under the three drug study conditions was completed Monday, Wednesday, and Friday. Participants remained on-site and under medical supervision after data collection for continued monitoring and sufficient drug elimination prior to daily release. The interim Tuesday and Thursday were reserved for drug wash-out and rest. The order of drug administration was initiated with a roll of a six-sided dice, then completed in a pseudo-randomized Latin square ensuring even participant numbers per drug group (eight participants in each of six drug order groups). Vital signs including pulse, blood pressure, respiratory rate, and oral temperature were monitored. Symptom questionnaires were administered by technicians preintervention and at intervals of 10 min, 40 min, 70 min, 4 h, and 8 h postintervention (Table 2).

Test Metrics

Testing was designed to evaluate performance on representative military tasks—basic but essential skills that all soldiers must be able to perform in an operational environment. These tasks were selected from a larger group forming the baseline of military competence in the field. They provide an opportunity to assess vigilance, critical thinking, judgment, and skilled performance within a military context. Military tasks were completed immediately after drug administration (intervention). See section below for statistical approach.

Table 2. Symptom Checklist*

Nervousness	Feelings of excitement	Jitteriness
Feelings of aggression	Feelings of happiness/elation	Tiredness
Dizziness	Racing heartbeat	Pounding of heart or heartbeat
Headache	Nausea	Vomiting
Tremor	Double vision	Blurred vision
Itching	Disordered thought	Poor concentration
Unreal thoughts	Any noticeable drug effect	Other (state)

* Symptoms coded as “no” = 0, “mild” = 1, “moderate” = 2, “severe” = 3.

Figure 1. Engage targets with an M16 or M4 series rifle. (Note: face intentionally blurred.)

Engage targets with an M16 or M4 series rifle. Participants completed the U.S. Army standard marksmanship qualifying task on the Engagement Skills Trainer (EST) 2000. The EST 2000 is the U.S. Army’s small arms training device and part of basic rifle marksmanship training strategy. The EST 2000 consists of an instructor-operator station, a high-resolution projector, a detection system, an air compressor, a screen, cabling, and hoses to connect to lane position weapon boxes, and the associated small arms weapons. The weapons are slightly modified to interface with the system but still maintain their form, fit, feel, and function (Figure 1). Dependent measures included number of hits, reaction time to trigger pull, shot radius from target center of mass (CM), and root mean square (RMS) of the aim trace.

Shoot-don’t shoot (identify targets). Using the EST 2000 9-mm sidearm, participants completed a friend/foe/neutral shoot/don’t shoot detection task. Metrics included number of hits, reaction time to trigger pull, shot radius from target CM, and RMS of the aim trace.

Correct malfunctions of an M16 or M4 rifle series. Correct rifle malfunction is commonly referred to as the acronym SPORTS for the subtasks: 1) Slap upward on the magazine to ensure its seated, 2) Pull the charging handle back, 3) Observe the ejection of the cartridge and check for obstructions, 4) Release the charging handle to feed another round into the chamber, 5) Tap the forward assist, and 6) Squeeze the trigger. Metrics included task accuracy and time to completion.

Mission-Oriented Protective Posture (MOPP) gear and protective mask (Promask). MOPP tasks were divided into four subtasks in accordance with each of the

Figure 2. Protection of self using the Promask (Umeå, Sweden). (Note: eyes intentionally blurred.)

MOPP levels: 1 = don trousers and jacket; 2 = don overboots, 3 = don protective mask, and 4 = don protective gloves. Protection of self using the Promask was divided into two tasks. The first task entailed donning, clearing, and checking the protective mask, and the second task entailed securing the hood (Figure 2). Metrics included task accuracy and time to completion.

Perform voice communications/radio task and request medical evacuation (MEDEVAC). Participants were presented with disassembled parts of an AN/PRC-90 handheld radio and tested on speed and accuracy of bringing the radio to mechanical functionality and entering the radio net using correct call signs, sequence, prowords, and phonetic alphabet and numerals. Participants were also required to interpret a basic casualty scenario, extract pertinent information, and transmit a standard 9-line MEDEVAC request providing necessary information and using proper brevity codes. The 9-line was separated into two tasks: task 1 consisted of MEDEVAC lines 1–5 (must be completed within first 25 s of radio transmission) and task 2 consisted of lines 6–9 (no time limit for completion). Metrics included task accuracy and time to completion.

In addition to the soldier skill tasks, the Evaluation of Risks Questionnaire (EVAR), a measure of risk propensity (yields three subscale scores [*risk/thrill seeking*, *need for control*, *self-confidence*] and a total score) was administered at baseline and then midway between completion of soldier tasks for each dose day (26).

Statistical Analysis Approach

All dependent measures were baseline-adjusted by subtracting one's baseline score from each of the three drug conditions. The independent variable (IV; within subjects) used in most analyses was *drug*; morphine, placebo, and ketamine. For marksmanship data, *target distance* is a within-subjects factor with six levels (50 meters [m], 100 m, 150 m, 200 m, 250 m, and 300 m).

Marksmanship tasks (standard qualifying and friend/foe). Data were analyzed using 6 (*target distance*) × 3 (*drug*) repeated-measures analyses of variance (ANOVAs).

Skill tasks. Error rates were analyzed using a χ^2 test, and the performance times (time to complete) were analyzed using repeated-measures ANOVAs (IV: *drug*).

EVAR. The total and three sub-scale (*risk/thrill-seeking, need-for-control,* and *self-confidence*) scores were analyzed using a repeated-measures multivariate ANOVA (IV: *drug*).

RESULTS

Test Metrics

Engage targets with an M16 or M4 series rifle. Thirty-two participants were included in the data analysis. Fifteen participants were excluded for incomplete data due to simulator technical malfunction, and one subject did not receive one of the drug conditions due to medical reasons. There were no significant main effects of *target distance* or *drug condition* on the dependent variables (reaction time, shot radius, proportion of hits, and aim trace), nor were there significant interactions. It should be noted that the EST 2000 rifle data were also broken out by shooting position (kneeling, prone supported, prone unsupported) for analysis, as well, none of which yielded significant results.

Shoot-don't shoot (identify targets). Thirty-two participants were included in the data analysis. Fifteen participants were excluded for incomplete data due to technical malfunction and one subject did not receive one of the drug conditions due to medical reasons. For the shot radius data, the assumption of sphericity was violated and a Greenhouse-Geisser correction was used. There were no significant main effects of *drug condition* on any of the four dependent measures.

Correct malfunctions of an M16 or M4 rifle series. A total of 46 participants were included for analysis. A χ^2 test was conducted on the accuracy of the SPORTS task with three conditions (ketamine, morphine, and placebo),

yielding no significant differences. A within-subjects ANOVA was conducted on the performance times of the SPORTS task (IV: *drug*) and was not significant.

Mission-Oriented Protective Posture gear and protective mask (Promask). Forty-six participants were included in the analysis. The results of the four independent χ^2 tests conducted to evaluate the accuracy of the four MOPP subtasks did not reveal significant differences between drug conditions. The results of the ANOVAs showed a significant main effect of *drug* on mean performance time on all four tasks; task 1, $F(2, 90) = 15.715$, $p < 0.001$; task 2, $F(2, 90) = 14.771$, $p < 0.001$; task 3, $F(2, 90) = 13.545$, $p < 0.001$; and task 4, $F(2, 90) = 17.301$, $p < 0.001$. Bonferroni-corrected pairwise comparisons ($\alpha = .05/3 = .017$) were conducted on the results of each MOPP task and found ketamine to be significantly different from both morphine and placebo in all four parts of the task (all significance levels were $p = 0.001$ or less) such that participants were slower with ketamine than morphine or placebo (Figure 3).

The χ^2 tests showed that accuracy did not differ between drug conditions on the two Promask tasks. However, the results of the ANOVAs did show a main effect of *drug* on mean performance times for Promask task 1, $F(2, 69.911) = 4.004$, $p = 0.032$, (Greenhouse-Geisser corrected), but not for Promask task 2. Bonferroni-corrected pairwise comparisons showed that participants were slower with ketamine ($p = 0.002$) than with morphine (Figure 4).

Perform voice communications/radio task and request medical evacuation. Data from 46 participants were included in the analysis. The result of the χ^2 test on the radio task accuracy was not significant, nor was the result

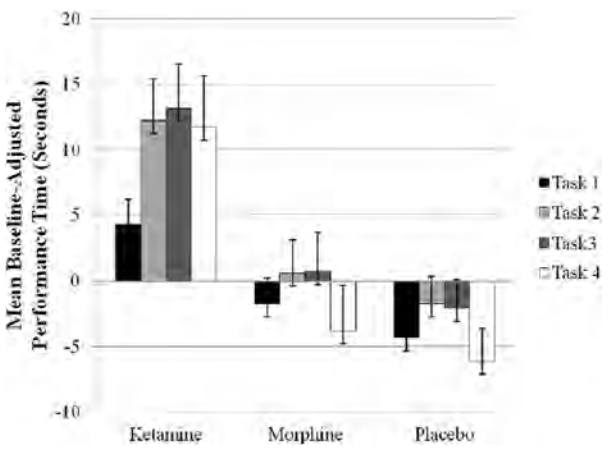

Figure 3. Mean baseline-adjusted performance times (seconds) for Mission-Oriented Protective Posture tasks 1–4. Error bars represent standard error of the mean.

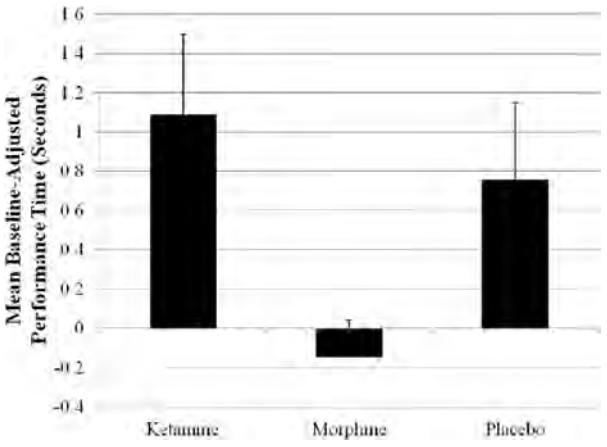

Figure 4. Mean baseline-adjusted performance times (seconds) for Promask task1. Error bars represent standard error of the mean.

of the ANOVA on mean performance times. For the requested MEDEVAC task, the χ^2 analysis result was not significant for task 1 but did yield a significant result for task 2, such that participants performed fewer errors with morphine and placebo compared to baseline; $\chi^2 (4, N = 46) = 11.016$, $p = 0.026$. No significant differences resulted from the ANOVA for task 1, however, there was a significant main effect of *drug* for task 2, $F(2, 88) = 5.368$, $p = 0.006$, such that participants performed faster with morphine and placebo than ketamine, (Bonferroni-corrected pairwise comparisons, $p = 0.006$ and $p = 0.012$, respectively) (Figure 5).

Vital signs and symptoms. Although not a primary outcome objective of this study, subjects' vital signs and subjective symptom scores were taken preintervention and at intervals of 10 min, 40 min, 70 min, 4 h, and 8 h postintervention. Ketamine resulted in higher systolic and diastolic pressures at 10 min (roughly 15% increase) and 40 min (roughly 5% increase) after dosing. Likewise, ketamine resulted in a higher pulse rate at 10 min postdose (roughly 15% increase). Overall, the symptoms most often reported for ketamine were dizziness, poor concentration, and feelings of happiness, compared with morphine, which included tiredness, feelings of happiness, and nausea. Throughout, regardless of severity, subjects reported more symptoms after ketamine than with morphine or placebo. Other symptoms with ketamine included nervousness, jitteriness, feelings of happiness/elation, dizziness, headache, double vision, blurred vision, disordered thought, poor concentration, and noticeable drug effect. All of these symptoms, with the exception of headache, were characterized by improvement (or stability in the case of nervousness and jitteriness) at the +40-min mark and return or near return to baseline by the +70-min mark.

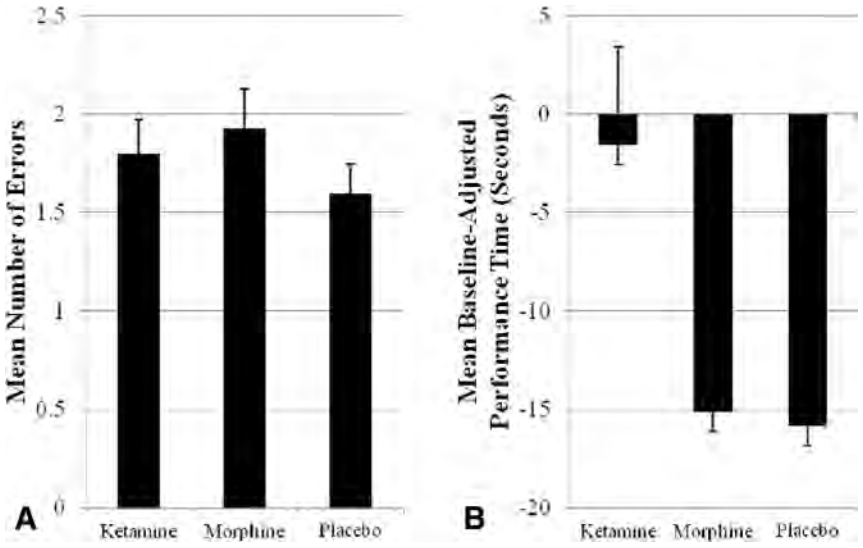

Figure 5. (A) Mean baseline-adjusted performance times (seconds) and (B) mean number of errors for MEDEVAC request task 2. Error bars represent standard error of the mean. MEDEVAC = medical evacuation.

EVAR. Forty-three participants were included in the analysis. Four participants were excluded from the analysis for incomplete data resulting from failure to respond to all questions in the assessment, and one subject did not receive one of the drug conditions due to medical reasons. For the *risk/thrill-seeking* sub-scale scores, there was a significant effect of *drug*, $F(2.15, 90.36) = 11.60$, $p < .001$. Paired comparison *t*-tests revealed that subjects showed a significantly greater change from baseline in the ketamine condition than in the morphine ($p = 0.003$) or placebo ($p = 0.001$) conditions. In the morphine condition, subjects showed a negative change in scores contrary to the positive change in the placebo condition ($p = 0.033$) (Figure 6).

Also, there was a significant effect of *drug* on *self-confidence* scores, $F(2.11, 88.65) = 10.64$, $p = .001$. Subsequent paired comparison *t*-tests showed that in the ketamine condition, participants' confidence decreased from baseline significantly more (thus, a larger difference in scores) than in the morphine ($p = .008$) and placebo ($p = .001$) conditions.

Finally, there was no significant effect of *drug condition* on baseline-adjusted *need-for-control* scores, but there was a significant effect of *drug* on baseline-adjusted total EVAR scores, $F(1.96, 82.45) = 11.04$, $p < .001$. Specifically, in the ketamine condition, participants' total risk propensity score decreased from baseline significantly more (thus, a larger difference in scores) than in the morphine ($p = .003$) and placebo ($p = .001$) conditions, as shown by paired comparison *t*-tests. Also, in the morphine condition, baseline-adjusted scores decreased significantly more than in the placebo condition ($p = .040$).

DISCUSSION

This study was conducted to characterize the effects of a single i.m. dose of 25 mg ketamine (the bioequivalent dose of 60 mg i.n. ketamine) vs. the current analgesic standard of 10 mg i.m. morphine (vs. a placebo control) in the performance of representative military tasks in healthy volunteers. Study metrics included an evaluation of risk propensity and multiple soldier skill tasks tested for speed and accuracy.

Performance Tests and Soldier Skill Tasks

Subjects reported more symptoms with ketamine than morphine or placebo, and one might expect decrements in task performance in the form of more errors and increased performance time. Indeed, given the nature of the symptoms reported (e.g., blurred vision, dizziness), it would be reasonable to expect subject difficulty with many aspects of the testing. However, decrements on ketamine, when present, were relatively underwhelming.

Engagement Skills Trainer (EST) 2000. Basic rifle marksmanship, arguably one of the most fundamental skills required of all soldiers, failed to demonstrate significance for any shooting position (prone supported, prone unsupported, or kneeling) for any of the metrics (target hits, reaction time, CM shot distance, or RMS of aiming trace). This was particularly unexpected given the subjective symptoms of double and blurred vision, poor concentration, and disordered thought.

The results of the EST 2000 suggest that subjects' performance on the weapons simulator was unaffected by

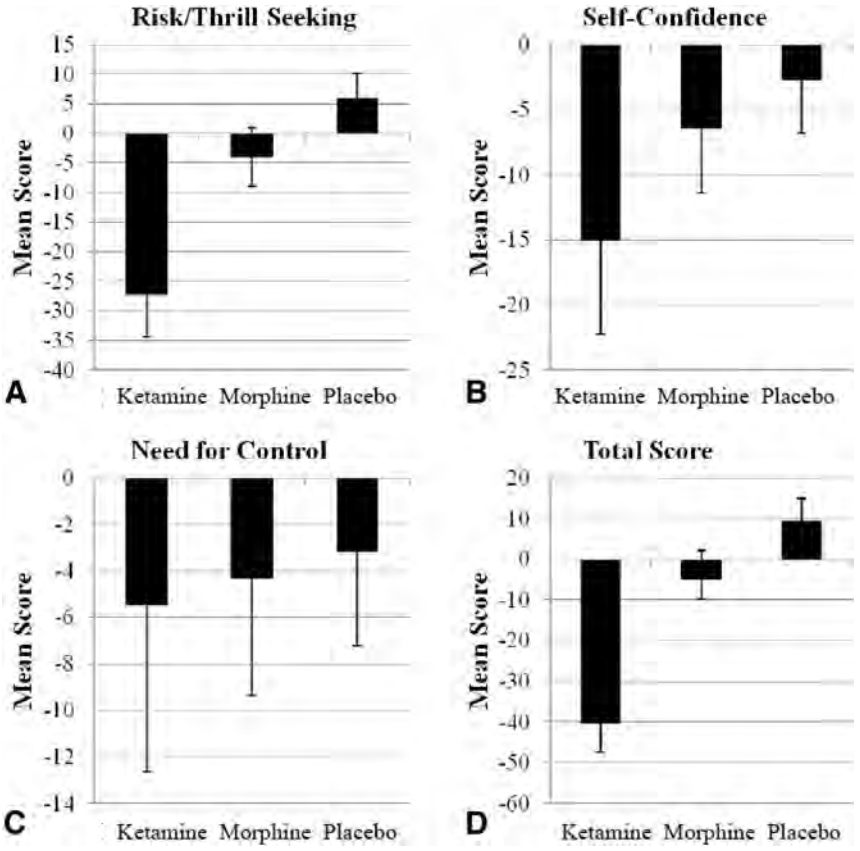

Figure 6. Mean baseline-adjusted Evaluation of Risks Questionnaire scores: (A) *Risk/thrill-seeking*, (B) *Self-confidence*, (C) *Need-for-control*, and (D) Total score. Error bars represent standard error of the mean.

drug at this dose. However, there are a number of factors to be considered. First, 15 subjects' data were lost due to technical malfunction of the EST 2000, and one subject was excluded for medical reasons (withheld dose). One interpretation of these statistics is that the resulting sample of usable data was insufficient to detect a difference if one truly exists in the population. Not only would an increase in sample size increase statistical power, but it would also narrow the confidence interval, thus providing a better estimate of the true population value.

An alternative explanation is that at these dosages, there are no effects of ketamine (or morphine) on marksmanship performance. Preliminary evidence suggests that visuospatial memory and ability, which play a role in marksmanship performance, are cognitive functions that have been shown to be unaffected by ketamine, thus supporting the lack of marksmanship impairment seen in this study (27,28). Likewise, previous studies have found that, although recall memory, working memory, and acquisition processes have been impaired by ketamine, recognition memory (a form of declarative memory) remains intact (29). Recognition memory—one's ability to remember something that has previously been experienced—has implications for performance on the weapons simulator (a familiar training scenario), which may therefore be unaffected by ketamine. However, marksmanship (as well as other basic soldier tasks) is also a learned skill that is considered procedural memory, an aspect of cognition that has not been explicitly tested with ketamine. Therefore, further testing may be necessary to fully understand the relationship between marksmanship and pharmacological agents like ketamine.

It should be noted that previous research suggests that effects of ketamine on memory, behavior, and cognition are dose-dependent, such that higher doses (e.g., 75 mg) produce impairments not seen in lower doses (28,30). A larger dose may very well have produced impairments in marksmanship performance.

Correct malfunctions of an M16 or M4 series rifle. The SPORTS malfunction task consisted of six simple sequential steps to correct a stimulated weapon stoppage. Baseline corrected mean error rates and performance times failed to demonstrate significance by drug condition, suggesting that acquired skill was unaffected by the administered drugs. In agreement with the results of marksmanship performance, it is reasonable to conclude

that the procedural task was retained despite drug administration at this dose. However, caution must be taken in the interpretation of these results given that the soldier skill tasks are not validated measures of cognitive function.

Don protective mask and MOPP. Divided into two tasks consisting of donning, clearing, and checking the mask (task 1) and donning hood ensemble (task 2), the drug condition did not yield significance for accuracy for either task. Regarding speed, significance was found for task 1 only. It is unclear how to interpret this, however, given that subjects were slower on ketamine vs. morphine, but not placebo. Furthermore, mean performance times were faster for all three drug conditions compared to baseline for task 2, suggesting continued learning (training did not quite reach asymptote on day 1).

Divided into four tasks corresponding with each of the MOPP postures, drug condition failed to demonstrate significance for accuracy for any of the four tasks. However, ketamine did significantly slow task performance time for all four tasks for both morphine and placebo, adding a mean total time of roughly 40 s. This task requires little cognitive ability or executive function, and this is most likely attributed to symptoms of dizziness, postural instability, and poor concentration. Indeed, many subjects were observed to sit on the floor to don MOPP trousers and boots, whereas they could easily balance on one leg upright at baseline. Furthermore, as described with the EVAR discussion, subjects may have proceeded with slightly more caution armed with the awareness of their impaired state. Nonetheless, errors were not a consequence. The finding that performance speed was slowed but accuracy was spared is consistent with previous research (28).

Perform voice communications and request medical evacuation. Radio assembly, voice communications, and the 9-line MEDEVAC tasks all failed to demonstrate significance for drug condition with the exception of task 2 of the MEDEVAC (lines 6–9). With respect to task 2, subjects on ketamine performed close to baseline for error and performance time, but morphine and placebo groups performed better than baseline (fewer errors and faster) in both respects. This improvement again suggests task learning.

The lack of significance for performance decrements on ketamine for task 1 (lines 1–5) of the MEDEVAC 9-line is interesting. Lines 1 through 5 include judgments and decisions regarding determination of pickup site, identifying patient by precedence, extracting frequencies and call signs, identifying requirement for special equipment, and others. Perhaps more so than any other task (shooting, donning mask and MOPP gear, immediate action malfunction drills, etc.), this task was judged to be the most complex, with a wide margin for error. Participants were required to analyze the scenario, extract pertinent information, make judgment and value determinations, and exhibit selective attention to only the relevant details. However, this task failed to demonstrate any significance among the drug conditions.

Skill tasks summary. All subjects received training and repetitive testing to asymptote for tasks on the first day prior to baseline testing and dosing later in the week. Basic soldier skill training, by design, is often repetitive in nature for skill acquisition and automaticity (especially desirable under extremely stressful or chaotic conditions such as combat). Despite the fact that subjects were more symptomatic on ketamine, the representative military tasks were largely resistant to performance decrements, suggesting that a trained task skill (the autonomous phase) is somewhat protected from the drugged state. And when decrements were present, they often manifested as slower performance times rather than procedural errors. This may represent a cautious state suggested by the EVAR, whereby the subject is aware of impairment and trades speed for preservation of accuracy.

Vital Signs and Symptoms

Although not a primary focus of this study, subjects' vital signs and subjective symptom scores with ketamine were largely consistent with dose-dependent expectations from the known pharmacodynamic delineation and side-effect profile. This may include vestibular impairment, perceptual distortions, dissociative effects, nystagmus, euphoria, and others. Cardiovascular effects include increased heart rate, stroke volume, vascular resistance, blood pressure, and catecholamines.

Evaluation of Risks (EVAR) Questionnaire

The results of the EVAR reveal differences among drug conditions that suggest changes in behavior given one's condition. Specifically, in both the morphine and ketamine conditions, subjects showed a decrease in scores from baseline, suggesting a tendency to become more conservative in behavior and less risk/thrill-seeking. This decrease was greater in the ketamine condition than in the morphine condition. This pattern of behavior was consistent across risk propensity factors, however, not significant for the *need-for-control* scores. It is probable that these results are a reflection of subjects' self-awareness of physical and psychological state such that they recognize their impaired state and appropriately adjust their levels of acceptable risk.

Limitations

The study was designed to incorporate realistic military tasks, however, the subjects received the analgesic test articles in the absence of antecedent pain stimulus. The phenomenon of pain is exceedingly complex, not limited to simple ascending neurosignaling pathways. It occurs within a milieu of a multitude of neurotransmitters, chemical mediators, and modulators involving nociceptors, many types of fibers, the spinothalamic and spinoreticular tracts, the limbic system, and the cortex (4). Indeed, a significant pain stimulus itself, the resulting physiologic cascade, or the catecholamine-charged context of combat can all certainly affect soldier performance.

With respect to pharmacokinetics, ketamine has high lipid solubility and low protein binding with a relatively fast onset of effect. The peak effect occurs about 5 min after i.m. injection. After this rapid onset, the effect is terminated largely by redistribution (approximate half-life 11 min) from the central nervous system to slower equilibrating tissues (14,31). The task performance metrics in this study began immediately after the +10-min symptom questionnaire. This was designed to allow time for i.m. absorption and an immediate close observation safety check of each subject by the study physicians. The result, however, is that some portion of the testing likely occurred during post drug redistribution (depending on rate of absorption). In operational use, it may likewise be prudent to observe casualties closely during this initial postdose period.

Results must also be interpreted within the context of subject sample representation of the larger military force. For example, the average age of active duty officers and enlisted personnel within the Department of Defense are 35 and 27 years, respectively, whereas the average study age of officers and enlisted subjects in this study was essentially reversed at 28 and 35 years, respectively (32). Of the eight MOSs represented in the study population, five were aviation-related in some form (likely the result of the recruiting pool). One may plausibly make the criticism that this group represents a special subset of military forces, in general. Nonetheless, the performance metrics used are not considered MOS-specific military skills and are universally trained to standard for all soldiers.

Furthermore, with respect to study demographics, of military personnel serving in Operation Iraqi Freedom/Operation Enduring Freedom, 11% are female, whereas only 6% of the study subjects were female (32). Literature supports a higher incidence of psychomimetic reactions and emergence phenomenon in females, whereas other studies have failed to demonstrate a gender influence to drug response (33–35). An often-cited reservation in using ketamine is the tendency toward psychomimetic reactions or emergence phenomena as the patient "reconnects" to sensory input. Incidence ranges widely in the literature (34,36). Much of the literature is directed at anesthetic-level dosing, however—much larger than dosage for this study. These reactions are reported to be more common in individuals with a psychiatric diagnosis or psychological susceptibility (33). This study population was screened for absence of this medical history for safety purposes. Furthermore, for safety reasons, potential subjects with a multitude of other medical conditions, some of which may have increased the side-effect profile or increased tendency toward complications, were also excluded.

As mentioned, the military task training and repetitive testing to asymptote prior to the drugged conditions later in the week could have induced or reinforced the autonomous phase of skill acquisition for the soldier tasks. This may have highlighted a relative resistance to performance decrements. Incorporating tests of basic cognitive function (e.g., working memory, acquisition process, higher-order executive function) would help clarify the effects of the 25-mg ketamine and 10-mg morphine doses on these processes as they might relate to soldier performance.

CONCLUSION

The 25-mg i.m. dose of ketamine did not result in better performance on soldier tasks compared to 10 mg of i.m. morphine in healthy volunteer subjects. Performance decrements on ketamine, when present, manifested as slower performance times rather than procedural errors. This may represent the adoption of a cautious posture, whereby the subject is aware of impairment, trading speed for preservation of task accuracy. Despite the fact that subjects were more symptomatic on ketamine, the skill tasks were largely resistant to performance decrements, suggesting that a trained task skill (autonomous phase) remains somewhat resilient to the drugged state at this dosage.

Acknowledgments—The authors would like to acknowledge the dedication and professionalism of the research staff of the Warfighter Health Division, U.S. Army Aeromedical Research Laboratory, for their contributions to this project. This study was funded by the U.S. Army Medical Research and Materiel Command's Combat Casualty Care Research Program. A detailed technical report of this study is available by contacting the USAARL Science Information Center at 334-255-6907. The study was approved by the U.S. Army Medical Research and Materiel Command Office of Research Protections Institutional Review Board. There are no financial or other relationships that may be perceived as a conflict of interest. This study was sponsored by the U.S. Army Combat Casualty Care Research Program.

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ARTICLE SUMMARY

1. Why is this topic important?

Prehospital care under remote, austere conditions may require that an individual continue with purposeful actions despite traumatic injury. Similarly, it may be necessary for a military casualty to remain engaged in soldier tasks after being wounded.

2. What does the study attempt to show?

The study attempts to delineate performance deficits in basic soldier skills comparing the military standard of 10 mg intramuscular (i.m.) morphine with 25 mg of i.m. ketamine. Study metrics included an evaluation of risk propensity and multiple soldier skill tasks tested for speed and accuracy.

3. What are the key findings?

Performance decrements on ketamine, when present, manifested as slower performance times rather than procedural errors. These deficits may represent the adoption of a cautious posture, as suggested by risk propensity testing whereby the subject is aware of impairment, trading speed for preservation of task accuracy.

4. How is patient care impacted?

These results will help inform the military casualty care community as well as those practicing prehospital care in austere environments regarding patient functional expectations after use of low-dose ketamine analgesia after wounding or traumatic injury.