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Feasibility and Safety of Oral Risperidone to Treat Prehospital Agitation

Nicholas S. Simpson^{a,b}, Alexander M. Schin^a, Michael C. Perlmutter^a, Alec J. Bunting^{a,b}, Gregg A. Jones^{a,b}, Holly M. Drone^{a,b}, Florian Merkle^{a,b}, Timothy M. Kummer^{a,b}, Brian E. Driver^a, Jon B. Cole^a, and Aaron E. Robinson^{a,b}

^aDepartment of Emergency Medicine, Hennepin Healthcare, Minneapolis, Minnesota; ^bHennepin EMS, Hennepin Healthcare, Minneapolis, Minnesota

ABSTRACT

Objective: Agitation is a common prehospital problem and frequently presents without a clear etiology. Given the dynamic environment of the prehospital setting, there has historically been a varied approach to treating agitation with a heavy reliance on parenteral medications. Newer best practice guidelines recommend the incorporation of oral medications to treat patients experiencing agitation. Therefore, we evaluated the use of oral risperidone in a single system after a change in protocol occurred.

Methods: This was conducted as a retrospective chart review of an urban/suburban Emergency Medical Services system over the period of 8 months. The first day this medication was implemented throughout the service was included. Charts were included for selection if they included risperidone oral dissolving tablet (ODT) as a charted medication. The primary outcome was administration of additional medications to treat agitation. Exploratory outcome measures included acceptance of medication, documented injury to paramedics, documented injuries to patients, scene times, and adverse events that could possibly be linked to the medication.

Results: A total of 552 records were screened for inclusion. Risperidone was offered to 530 patients and accepted by 512 (96.6%). Of these 512 patients, the median age of included patients was 39 years old (IQR 29–52 years old) with a range of 18–89 years old. Rescue or additional medications for agitation were required in 9 (1.8%) cases. There were a total of 4 (0.8%) potential complications following administration of risperidone. There were no reported assaults with subsequent injuries to prehospital personnel or injuries sustained by patients reported in this study.

Conclusions: Risperidone ODT was found to be a safe and effective medication to treat mild agitation in a large urban and suburban EMS system. The need for additional medications to treat agitation was rare, and there were no documented injuries to either patients or paramedics.

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Introduction

Agitation is a common problem in the prehospital environment and the emergency department (ED) (1–3). The exact etiology of agitation is often unknown, particularly in the prehospital environment, and while psychiatric causes and intoxication are the most common causes (4), agitation may also be due to metabolic, infectious, traumatic, and other toxicological causes (5, 6). While verbal de-escalation is generally recommended and employed as a first-line therapy (7), medications to treat agitation are often needed for both patient and caregiver safety (8). Given the dynamic environment of the prehospital setting, there has historically been a varied approach to treating agitation with a heavy reliance on parenteral medications (8–10).

In February 2012, the American Association for Emergency Psychiatry (AAEP), using an interdisciplinary panel of emergency physicians, emergency psychiatrists, and other emergency mental health professionals, published guidelines for Best practices in Evaluation and Treatment of

Agitation, known as Project BETA (11). These guidelines include recommendations for the psychopharmacologic treatment of agitation (12). Two of the guiding principles of Project BETA, and emergency psychiatry in general, are avoiding coercion and treating patients in the least restrictive setting possible (11). Both principles relate to medication selection when treating agitation and helped guide Project BETA to recommend oral medications as first-line pharmacologic treatments for agitation (11). These guidelines are supported by randomized trials demonstrating that oral medications are equivalent to intramuscular medications for calming agitated patients in in-hospital settings (13–16). Orally disintegrating tabs (ODTs) used for acute agitation should be rapidly absorbed with a short time to peak plasma concentration. Risperidone ODTs have all of these characteristics (17). Randomized trials have shown risperidone ODT to be equivalent to intramuscular haloperidol for treatment of agitation, both as monotherapy (14, 15) and in combination with lorazepam (13).

Data on the use of oral medications to treat agitation in the prehospital setting, however, is lacking (18). Additionally, as clinical practice evolves there are large organizations such as the American College of Emergency Physicians that recommend a better understanding of the use of oral medications for agitation (18). Therefore, the purpose of this study was to describe the use of risperidone ODT to treat mild agitation in the prehospital environment, defined as patients who are not posing any immediate threat to safety and who are redirectable.

Methods

Study Design and Setting

This retrospective cohort study of risperidone ODT was conducted at Hennepin EMS, which is an urban/suburban Emergency Medical Services (EMS) system that covers a service area of 266 square miles and 14 municipalities within Hennepin County, Minnesota. It serves a resident and visitor population of nearly 1.5 million people. Ambulance responses are all single-tier advanced life support (ALS) with each ambulance staffed by two paramedics. The service responds to nearly 100,000 annual calls for service; approximately 60,000 of these result in transport to a hospital. The EMS system is affiliated with Hennepin Healthcare, a Level I adult and pediatric trauma center and county safety net hospital in downtown Minneapolis, MN. In May 2021, the EMS formulary was updated based on Project BETA recommendations (12), to offer risperidone ODT for treatment of behavioral emergencies. The protocol is included as [Supplemental Appendix 1](#) for reference. Risperidone ODT was provided either one or two 2 mg orally disintegrating tablets for a total dose of either 2 mg or 4 mg.

Prior to implementation across the entire system, there was service-wide education of the approximately 165 paramedics. This consisted of a 12-min online video module and approximately 15 min of in-person teaching at a semiannual educational session. Paramedics were trained to use this treatment for mild agitation in patients who were redirectable. If there was an acute safety concern, this medication was not recommended. Additionally, the medication reference sheet available to all paramedics is included as [Supplemental Appendix 2](#).

This study was approved by the local institutional review board. As this was a retrospective chart review and deemed minimal risk, the requirement for informed consent was waived. Additionally, we report our findings in accordance with Standards for Quality Improvement Reporting Excellence (SQUIRE) 2.0 guidelines (19).

Selection of Participants

Participants were screened for inclusion if charts included risperidone as a documented medication (either given or not given) after May 5, 2021 and before March 1, 2022. The date was selected as it was the first date of the implementation of this medication for the service. Patients were

excluded if they were less than 18 years old, had an incomplete chart, or were not transported to the hospital.

Patients who were offered risperidone ODT but who declined the medication or spit it out were tallied but did not undergo further data collection. The remaining eligible patients underwent detailed data collection.

Methods of Measurement

Two physician abstractors (AS and MP) performed structured reviews of data from SafetyPad (SafetyPad Inc., Austin, Texas, USA) and entered data into Redcap (20). This included the time stamps, other interventions including medication administrations, and narrative portions of the chart.

The variables that were included were: date of service, patient age (years), patient sex, scene response code (i.e. routine driving = code 2, emergent driving = code 3), specific scene times captured in the chart (most frequently obtained by the geolocation of the ambulance, with the exception of the 'at patient time' and could be corrected by the crew if there was a technical issue), time of first risperidone ODT, dose of first risperidone ODT, any other medications administered throughout the care, transport code (i.e. routine driving = code 2, emergent driving = code 3), any documentation of unexpected events (e.g. possible complications), and report of injury to paramedic or patient, and primary impression. The abstractors reviewed the entirety of the chart to look for complications, which was defined as any unexpected events possibly linked to risperidone administration. This definition was broad to capture all potential complications.

Study Outcomes

The primary outcome was administration of additional medications to treat agitation. This was defined as any further prehospital administration of medications from the behavioral emergency protocol after risperidone was administered.

Exploratory outcome measures included the number of patients who accepted the risperidone ODT offered to them by the treating paramedic on scene, documented injury to paramedics at any point in the care, documented injuries to patients at any point in care, scene times, primary impression, and complications after medication administration.

Statistical Analysis

We used descriptive techniques to analyze the data, presenting counts and percentages or medians and interquartile ranges (IQRs) as appropriate. We estimated the imprecision of the primary outcome estimate with a 95% confidence interval. To assess for interobserver agreement, 10% of charts were reviewed by a second reviewer for the occurrence of the primary outcome (additional medication for sedation) and the occurrence of complications. Agreement for the primary outcome was 100% with a κ value of 1.0. In both the initial data set and second reviewer data set, there

was also perfect agreement with no instances of injuries to the patient or staff. All statistical analyses were performed with Stata (version 15; StataCorp, College Station, TX).

Results

Characteristics of Study Subjects

A total of 552 records were screened for inclusion and 22 were excluded (Figure 1). Risperidone was offered to 530 patients and accepted by 512 (97%). Of the 512 patients that accepted risperidone, the median age of included patients was 39 years old (IQR 29–52 years old) with a range of 18–89 years old (Table 1). The median time (MM:SS) from EMS arrival on scene to arrival at the patient was 01:25 (IQR 00:26–03:27). The most common doses administered were 2 mg or 4 mg (54.3% and 43.9%, respectively), which is consistent with the agency protocol.

Main Results

Additional medications administered to treat agitation were documented in a total 9 (1.8%, 95% CI 0.8% to 3.3%) cases. The average time (MM:SS) between risperidone

administration and any additional medication to treat agitation was 07:00 (IQR 4:00–13:00, range 0–26). Droperidol and midazolam were the only drugs used after risperidone (Table 2).

There were no reported assaults with subsequent injuries to prehospital personnel or injuries sustained by patients reported in this study (Table 3).

There were 4 (0.8%) potential complications after administration of risperidone. One patient who was not initially complaining of nausea developed nausea. This patient received 2 mg risperidone. It is possible that this was related to the taste of the medication. The remaining three complications are detailed below and include hypoglycemia, seizure with subsequent hypoxia, and apnea that responded to naloxone (Table 3).

A 43-year-old male with past medical history of substance and alcohol use disorders presenting with symptoms of alcohol withdrawal, had a blood glucose of 56 mmol/L 3:17 (MM:SS) after 2 mg risperidone administration. Given the patient's past medical history, presentation, and time between risperidone administration and hypoglycemia, it is unlikely that his hypoglycemia was directly related to risperidone.

The patient with the seizure and hypoxia was a 76-year-old female without a past medical history of seizures. She experienced seizure-like activity approximately 15 min after administration of 4 mg risperidone. The episode lasted for approximately 1 min and self-terminated. She became hypoxic to 36% on room air during this event which responded to 12 liters/min oxygen via non-rebreather mask. In U.S. Food and Drug Administration (FDA) label information for risperidone, there was a 0.3% (9 of 2607) incidence of seizure in the preclinical data, including two cases of concomitant hyponatremia (17). The rate of seizure from Droperidol in a similar population has been shown to be 0.12% from a large ED study (21). There was no evidence of QT prolongation from the FDA label information to suggest Torsades de Pointes is likely as seizure mimic, as is seen in other psychiatric medications (17). It is possible, though unclear if risperidone contributed to the seizure-like activity and hypoxia in this case given the patient's past medical history.

Another patient, a 52-year-old male with a report of Lysergic Acid Diethylamide (LSD) use and anxiety with paranoia, developed apnea after administration of 2 mg risperidone. The patient received naloxone 0.4 mg IV with improvement of respiratory status. Naloxone was given approximately 2:10 (MM:SS) after administration of 2 mg risperidone ODT, suggesting that this complication was not directly related to risperidone.

To better understand the clinical situations in which the medication is being utilized in the prehospital environment, the categories of the treating paramedic's primary impression are included in Table 4.

Discussion

We found risperidone was successfully administered to 512 patients with mild agitation and that additional medication

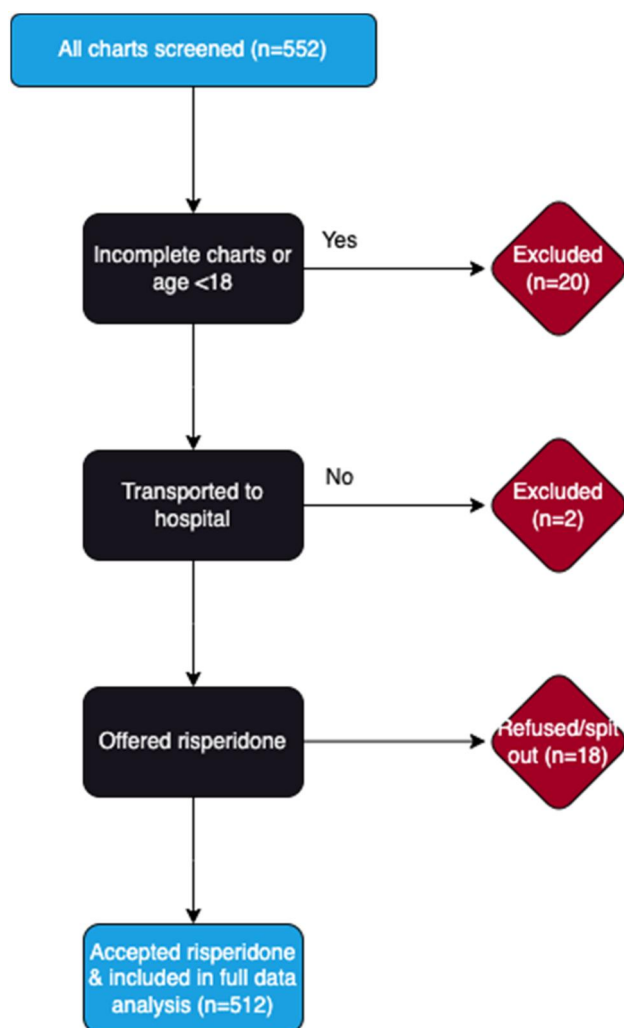


Figure 1. Diagram of charts screened and reasons for exclusion.

Table 1. Characteristics of patients and encounters included.

Characteristics	Number of patients (% of total) N = 512
Female sex	264 (52)
Male sex	248 (48)
Age, median (IQR, range), years	39 (IQR 29–52, range 18–89)
Risperidone dose	
1 mg	1 (<1)
2 mg	273 (53)
4 mg	237 (46)
8 mg	1 (<1)
Arrival at scene to patient time, median (IQR), min	1:25 (00:26 – 03:27)
Patient time to risperidone, median (IQR), min	12:06 (07:40 – 18:50)
Total scene time, median (IQR), min	14:14 (09:25 – 21:02)
Arrival code	
Non-emergent	177 (35)
Emergent	335 (65)
Departure code	
Non-emergent	507 (99)
Emergent	5 (1)

Table 2. Primary outcome measure. Additional medications administered after risperidone to treat agitation.

Additional medication administered to treat agitation	Number of patients (% of total) N = 512
Any additional medication	9 (1.8)
Droperidol	
2 mg	1 (0.2)
5 mg	6 (1.2)
10 mg	1 (0.2)
Midazolam	
1 mg	1 (0.2)
Time between risperidone and additional medication to treat agitation, median (IQR, range), min	7 (IQR 4–13, range 0–26)

Table 3. Exploratory outcome measures. Potential adverse events that occurred after the administration of risperidone. Documentation of injuries to paramedics.

Potential adverse events after administration of risperidone	Number of patients (% of total) N = 512
Any complication	4 (0.8)
Nausea	1 (0.2)
Hypoglycemia	1 (0.2)
Hypoxia/Seizure	1 (0.2)
Apnea	1 (0.2)
Injuries documented to paramedics	0
Injuries documented to patients	0

Table 4. Primary impression of the charts reviewed by category.

Primary impression from the treating paramedic by category	Number of patients (% of total) N = 512
Mental health or behavioral	335 (65)
Substance use	80 (16)
Pain or injury	45 (9)
Cardiac	11 (2)
Respiratory	11 (2)
Nausea, vomiting, or gastrointestinal	10 (2)
Weakness or malaise	6 (1)
Infectious disease	4 (1)
Hyper- or hypothermia	2 (<1)
Unspecified altered mental status	2 (<1)
Visual disturbance	2 (<1)
Other	2 (<1)
Diabetes	1 (<1)
Vaginal bleed	1 (<1)

to treat agitation was rarely needed. As a service, the addition of an oral medication option for agitation can lead to a beneficial change to the paramedic and patient dynamic. An oral medication is something that the patient is choosing to take, rather than being given by prehospital personnel. It also provides a less invasive means of administration

(compared to intramuscular injection). Involving the patient in this decision and having them participate in the choice may strengthen the therapeutic relationship between patient and paramedic. A total of 18 patients from the 530 that were offered, either refused risperidone or spit it out after administration.

Risperidone was chosen because it is available as an easily administered ODT and is particularly beneficial for patients who are not able or willing to swallow traditional tablets with water. Several studies have shown that it is well tolerated and as effective as other oral and intramuscular agents such as haloperidol and olanzapine (10–12). All oral risperidone formulations are rapidly absorbed, peak in approximately 1 h (17) and have effects on agitation scale scores within as little as 15 min (10–11).

The use of oral medications may also induce a placebo effect prior to the expected onset of action of the medication. Therefore, despite Hennepin EMS having shorter transport times than other parts of the country, oral medication was found to be a viable option that can be utilized by paramedics. The implementation of an oral option for prehospital agitation has been well received by patients, paramedics, as well as staff at receiving facilities.

Additional medications were rarely administered for agitation, suggesting that risperidone as a single agent was typically sufficient to treat the patient's agitation. The administration of additional medication to treat agitation occurred in 9 (1.8%) cases. Although ketamine is part of the Behavioral Emergency protocol and reserved for the most severe levels of agitation, no patients received ketamine for agitation in this series.

The incidence of possible complications associated with pre-hospital administration of risperidone in this study was exceedingly low (0.8%). The majority of patients experienced no complications during their pre-hospital course. There were no reported injuries to either pre-hospital personnel or to patients in transport in this study. Given the very low incidence of complications and no documented injuries to personnel or patients during transport, the use of prehospital risperidone administration for agitation appears to be safe and effective in adults with agitation in the prehospital environment.

Limitations

There are several limitations to this study. First, this study was performed as a chart review including only prehospital data, which precludes any information or conclusions regarding events and outcomes after hospital arrival. Additionally, this was a retrospective review was performed after the clinical practice was changed. We included data from the first day of service wide change to minimize selection bias that could have taken place as prehospital personnel became accustomed to the medication over time. It is possible that the medication was offered in other cases that were not captured due to errors in charting. Similarly, it is possible that in cases where doses fell outside the protocol, the doses listed were inaccurate and entered in error. This study utilized the narrative component of the chart as the source of information about patient or paramedic assaults. We acknowledge that lack of documentation of an assault or injury may not definitively represent a true absence of assaults or injuries during these encounters. This study does not include data from patients who were treated with

medications as part of the Behavioral Emergency protocol in the absence of risperidone. Finally, as a single center study, generalizability of these data may be limited.

Conclusion

In this retrospective chart review in a single prehospital system, the use of risperidone ODT is feasible to treat patients experiencing mild agitation who are not posing an immediate physical threat and are redirectable. It was found to be a safe and effective medication to treat mild agitation in a large urban and suburban EMS system. Complications following risperidone administration were rare and no injuries were reported to prehospital personnel or patients.

Disclosure Statement

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Declaration of Generative AI in Scientific Writing

The authors did not use a generative artificial intelligence (AI) tool or service to assist with preparation or editing of this work. The author(s) take full responsibility for the content of this publication.

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