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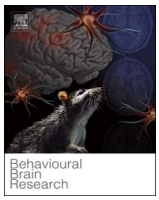

Research report

Spontaneous recovery of traumatic brain injury-induced functional deficits is not hindered by daily administration of lorazepam

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ABSTRACT

Agitation and aggression are common sequelae of traumatic brain injury (TBI) and pose a challenge to physicians and other health providers during acute patient care and subsequent neurorehabilitation. Antipsychotic drugs (APDs) are routinely administered to manage TBI patients displaying such maladaptive behaviors despite several clinical and preclinical studies demonstrating that they hinder recovery. A potentially viable alternative to APDs may be the benzodiazepines, which have differing mechanisms of action. Hence, the aim of the study was to test the hypothesis that lorazepam (LOR) would not impede recovery after TBI. Anesthetized adult male rats received a cortical impact or sham injury and then were intraperitoneally administered LOR (0.1 mg/kg, 1.0 mg/kg, or 2.0 mg/kg) or vehicle (VEH; 1 mL/kg) commencing 24-h after surgery and once daily for 19 days. Motor and cognitive outcomes were assessed on post-operative days 1–5 and 14–19, respectively. No differences were revealed among the four sham control groups and thus they were pooled into one inclusive SHAM group. The SHAMs performed better than all TBI groups on all assessments ($p < 0.05$). Regarding TBI, the 2.0 mg/kg LOR group performed better than the VEH and 0.1 mg/kg or 1.0 mg/kg LOR groups on every task ($p < 0.05$); no differences were observed among the latter three groups on any endpoint ($p > 0.05$). Overall, these preclinical behavioral data support the hypothesis and reveal a therapeutic benefit with the higher dose of LOR. The findings suggest that LOR may be an alternative, to APDs, for controlling agitation without compromising spontaneous recovery and perhaps could afford a dual benefit by also promoting therapeutic efficacy.

1. Introduction

An estimated 10 million people worldwide incur a traumatic brain injury (TBI) each year [1] that yields significant neurological disabilities and negatively impacts quality of life [2–8]. The financial burden resulting from medical and rehabilitative care, as well as diminished productivity, is estimated to be greater than $76.5 billion per year [2,3]. In addition to motor and cognitive dysfunction, which include, but are not limited to, postural and balance deficits as well as memory loss, impulsivity, poor executive function, and learning impairments [9–11], TBI induces agitation and aggression, with the former afflicting as many as 70% [12–15] and the latter affecting 34% of the clinical TBI population [16,17]. Moreover, these maladaptive behaviors may hamper acute medical care and subsequent neurorehabilitation [18].

To manage these behavioral dysfunctions, antipsychotic drugs (APDs) are routinely administered [12,18–23] with the intent to provide safety for both the patient and staff [18,20,24], as well as, to allow for greater patient participation in rehabilitation [25]. While haloperidol (HAL), which is a D_2 receptor antagonist, is effective in reducing the agitation [18,26,27], it hinders recovery as shown by several clinical studies [12,18–23]. Rao and colleagues (1985) showed that HAL extended the duration of post-traumatic amnesia in a group with severe traumatic closed head injury [28]. HAL has also been reported to

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induce neuroleptic malignant syndrome in a TBI patient [29]. Moreover, HAL reduced the degree of cognitive improvement after its discontinuation, suggesting long-term cognitive deficits with its use [22].

Persistent cognitive deficits have also been reported in pre-clinical studies assessing HAL and risperidone [30]. Specifically, HAL has been shown to halt the acquisition of spatial learning and memory as demonstrated by significantly slower and less learning over time vs. vehicle-treated controls [31,32]. These findings, in parallel with data showing that D_2 receptor agonists, such as bromocriptine and methylphenidate, enhance the recovery process [30,33–36] demonstrate that typical and atypical APDs are impairing functional recovery after TBI likely due to D_2 receptor antagonism mediated perturbations.

Despite the APD-induced deleterious effects on neurobehavior and cognition, some form of post-injury sedation is necessary to manage disruptive patients. Management of symptoms is critical to ensure patient and staff safety [18,20,24] as well as thorough patient evaluation and treatment. In the longer term, reducing agitation may facilitate optimal participation in neurorehabilitation [25]. Hence, alternative pharmacological treatments that may reduce agitation and/or aggression without compromising spontaneous recovery are warranted.

A potentially viable alternative to APDs may be the benzodiazepines, which have differing mechanisms of action. Lorazepam (LOR), for example, is a member of the classical benzodiazepine drug family that includes diazepam [37–40]. Benzodiazepines are positive allosteric modulators of GABA receptors and have no D_2 antagonism properties [37,38,40,41]. Because the mechanism of action for LOR differs from that of HAL and risperidone, it is hypothesized that LOR would not impede motor and cognitive recovery when provided chronically after TBI. While several excellent reviews and studies exist discussing the use and efficacy of benzodiazepines in general [42–44] and LOR specifically [26,45–49] to manage agitation after clinical brain injury, there are no experimental studies evaluating LOR after experimental TBI. Hence, the current study was designed to investigate a dose response of LOR on neuromotor and cognitive performance after cortical impact injury in rats. The rationale is that LOR, if innocuous to motor and cognitive recovery after TBI with doses that produce sedation, may be considered as a viable alternative to typical and atypical APDs after brain trauma.

2. Materials and methods

2.1. Subjects

Sixty-seven adult male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 300–325 g on the day of surgery were housed in ventilated polycarbonate cages and maintained in a temperature (21 ± 1 °C) and light controlled (on 0700–900) environment with food and water available *ad libitum*. The rats were acclimated to the colony for one week and then underwent a single day of beam-walk training until able to traverse the entire length of the beam (100 cm) within 5 s. Fully trained rats were then randomly assigned to one of four TBI or one of four sham groups where they received one of three doses of LOR (0.1 mg/kg, 1.0 mg/kg, or 2.0 mg/kg) or vehicle (VEH; 1.0 mL/kg). All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh. Every attempt was made to limit the number of rats used and to minimize suffering.

2.2. Surgery

A surgical level of anesthesia was induced and maintained with inspired concentrations of 4% and 2% isoflurane, respectively, in 2:1 N_2O:O_2 in a vented anesthesia chamber. Following endotracheal intubation, the rats were secured in a stereotaxic frame and mechanically ventilated. Utilizing aseptic techniques, a 6-mm craniotomy was made in the right hemisphere between bregma and lambda and from midline to the coronal ridge, using a high-speed dental drill. A controlled cortical impact (CCI) of 2.8 mm tissue deformation at 4 m/sec produced an injury of moderate severity as previously described [30–32,50–54]. Sham control rats underwent all anesthetic and surgical manipulations except the impact. Anesthesia was discontinued immediately after CCI or sham injury and the incision was promptly closed with nylon sutures. The rats were subsequently extubated and acute neurological evaluations were performed.

2.3. Acute neurological evaluation

Return of the righting reflex was determined by the time required to turn from the supine to prone position three consecutive times and was assessed immediately after the cessation of anesthesia.

2.4. Drug administration

LOR was purchased from Tocris Bioscience (Bristol, UK) and was prepared daily by dissolving in 1:1 dimethyl sulfoxide and physiological saline, which served as the VEH. LOR or a comparable volume of VEH was administered intraperitoneally beginning 24 h after CCI or sham injury and once daily until all behavioral evaluations were completed (i.e., post-operative day 19). On the days when behavioral assessments were conducted, treatments were administered immediately after testing by an experimenter unaware of group conditions. The exception to this paradigm was to determine if the doses utilized were sufficient to induce sedation, which would be necessary to reduce agitation and aggression clinically. In this instance, a sub-set of rats were administered LOR (2.0 mg/kg) or VEH and 1-h later swim speed was evaluated in the water maze. The route of administration was selected based on previous studies from our laboratory [30–32,51] and the LOR doses were selected from both the literature [55–58] and the aforementioned pilot study from our laboratory. Clinical doses are in a range of 2–4 mg/kg for control of agitation and aggression in adults [49] and 0.1–4 mg/kg for status epilepticus in pediatric patients [59,60].

2.5. Motor performance: beam-balance and beam-walk

Established beam-balance and beam-walk tasks were used to assess motor function. Briefly, the beam-balance task consists of placing the rat on an elevated and narrow beam (1.5 cm wide) and recording the time it remains on for a maximum of 60 s. The beam-walk task, modified from that originally devised by Feeney and colleagues (1982) [61], consists of training/assessing rats using a negative-reinforcement paradigm to escape a bright light (situated directly over the start point) and white noise by traversing an elevated narrow beam (2.5 × 100 cm) and entering a darkened goal box. The adverse stimuli (light and noise) were terminated when the rat entered the goal box, which served as reinforcement for completing the task. Performance was assessed by recording the elapsed time to traverse the beam. Rats were tested for beam-balance and beam-walk performance prior to surgery to establish a baseline measure and again on post-operative days 1–5. Testing consisted of three trials (60 s allotted time with an inter-trial interval of 30 s) per day on each task. If a rat was unable to traverse the entire length of the beam the maximum allowed time of 60 s was recorded. The average daily scores for each rat were used in the statistical analyses.

2.6. Cognitive function: acquisition of spatial learning and memory

Spatial learning was assessed in a water maze task demonstrated to be sensitive to cognitive function/dysfunction after TBI [30–32,51,62–66]. The maze was a plastic pool (180 cm diameter, 60 cm high) filled with tap water (21 ± 1°C) to a depth of 28 cm and was situated in a room with salient visual cues. The platform was a clear Plexiglas stand (10 cm diameter, 26 cm high) that was positioned 26 cm from the maze wall in the south-west quadrant and held constant for