Loxapine for Management of Delirium in Older Adult Surgical Patients

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Abstract: The use of antipsychotics for the treatment of post-operative delirium is often practiced after non-pharmacologic methods of re-orientation have failed. Loxapine is a drug with medium-potency antagonism at dopamine receptors and is used frequently at our institution for delirium. In this small uncontrolled open-label study, we provide early findings that it is effective at reducing the severity and duration of delirium in an older population and may be a reasonable alternative for management. Delirium Rating Scale (DRS-R-98) scores were recorded in 31 older adult surgical patients (mean age 72, 2/3 male). Treating physicians ordered loxapine according to clinical judgment. We monitored for extrapyramidal side-effects, QTc changes, and other adverse events. The mean maximum cumulative loxapine dose per day was 44mg (s.d. 31). DRS-R-98 score after 2 days of treatment (mean 10.19, s.d. 6.61) was significantly reduced compared to DRS-R-98 score at time of diagnosis (mean 18.68, s.d. 4.66) [$t(30) = 6.65$, $p < 0.001$]. The mean number of days to resolution of delirium was 3.2 (s.d. 2.5). Only 3 participants experienced very mild extrapyramidal symptoms and there was no significant difference between baseline QTc (mean 422ms, s.d. 19.86) and mean QTc during treatment (mean 426ms, s.d. 18.47) in a subsample for which QTc data were available [$t(11) = 0.45$, $p > 0.5$]. Although there are several limitations to this small uncontrolled open-label study, the findings suggest loxapine is a reasonable alternative in treating delirium in older adult surgical patients.

Keywords: Delirium, antipsychotic, loxapine, haloperidol, surgery, geriatrics, elderly.

INTRODUCTION

Delirium is common in older hospitalized patients on a general medicine ward [1,2] and the prevalence is even higher in post-operative settings. For example, Rudolph *et al*. [3] found an incidence of 52% in cardiac surgery patients aged 60 and over, while the incidence following hip repair has been reported to be over 60% in some studies [4]. Delirium is often distressing and frightening for patients and their families and can have significant impact on post-surgical management. The degree of distress from delirium is such that approximately 10% of ventilated ICU patients who experience delirium have diagnosable post-traumatic stress disorder at 3-month follow-up [5]. Reviews of the impact of delirium have linked it with increased mortality, morbidity, length of hospital stay, functional decline, loss of independence, and increased financial costs for both the individual as well as for the medical system [4,6-9]. Evidence has also been mounting over the last decade that delirium predisposes patients to increased long-term cognitive decline [10-11]. A review by Maclullich *et al*. [12] suggests relative uniformity in the literature on this unfortunate association, and the meta-analysis by Witlox *et al*. [13] provides a strong source of evidence of the associations between delirium and subsequent dementia, institutionalization, and death.

Although new strategies for prevention of post-operative delirium are being developed [14], the high prevalence of delirium and the impacts described above necessitate ongoing reconsideration of the treatment strategies that are currently available. Reasonable non-pharmacological interventions, aside from trying to find a reversible cause (e.g. infection), include frequent re-orientation, therapeutic cognitive activities, establishing a sleep protocol, early mobilization, rehydration, and ensuring patients have vision and hearing aids when needed [15]. However, management of post-operative delirium often requires additional pharmacological intervention. There are no medications that are "indicated" for the treatment of delirium.

Because delirium is hypothesized to be a hyperdopaminergic/hypocholinergic state, haloperidol, a potent dopamine antagonist with little anticholinergic effect, is the most commonly used agent for management of delirium. Its other advantages include the potential for intravenous administration and little autonomic effect. Interestingly, head-to-head comparison with chlorpromazine, a lower-potency dopamine antagonist with greater anticholinergic effect, showed no difference in effectiveness between agents [16] and some clinicians prefer more sedating

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E-ISSN: 2310-8231/17

antipsychotics for either reducing agitation or promoting sleep at night. Because comparisons between antipsychotics tend to not reveal significant differences in effectiveness [17], patient-specific variables may provide the best reasons for selecting one agent over another. A patient who presents with delirium in the context of significant anticholinergic medication burden may benefit more from haloperidol, while a patient with Parkinson's disease and poor sleep may benefit more from quetiapine at night. The more options we have for treating delirium, the better we are able to tailor management for individual patients.

As a mid-potency typical antipsychotic with atypical properties [18], loxapine provides relatively potent dopamine blockade along with significant sedation. We have found it to be useful for management of delirium, particularly in older adult surgical patients. Because of our positive experiences with it and the recent development of inhaled loxapine [19], we feel it is a medication worth adding to the general hospital psychiatrist's toolbox. To our knowledge, there is no existing literature on using loxapine to manage delirium. We employed an uncontrolled open-label study in post-operative older adults to begin formally assessing its utility.

METHOD

Participants

The study was approved by the University of British Columbia Providence Health Research Ethics board and consent was obtained from patients or their substitute decision makers. Research procedures were carried out in accordance with the Declaration of Helsinki. Diagnosis was by DSM-IV-TR and corroborated by the Delirium Rating Scale Revised-98 (DRS-R-98) [20]. Of 53 consecutive cases of post-operative delirium in adults aged 55 or older referred to the psychiatry service, 31 enrolled in and completed the study.

Procedure

Participants were assessed with the DRS-R-98 and the Extrapyramidal Symptom Rating Scale (ESRS) [21] at the time of diagnosis and then every 2 days until the DRS-R-98 fell below 10. Loxapine use was open-label and other medications were ordered as clinically appropriate. Baseline QTc was obtained for all participants and was compared with QTc during loxapine administration for participants who had subsequent ECGs.

Statistical Analysis

DRS-R-98 score at day 0 and day 2, and baseline and mean QTc during treatment were compared using paired-samples t-tests. A Pearson correlation examined the relationship between maximum total dose and QTc change.

RESULTS

Participant Demographics

Mean age was 72 (range 60-84) and 20/31 were men. Three were regular drinkers, but did not show signs of withdrawal. Six were regularly taking narcotic medications. Nine had a previous episode of delirium, 2 had very mild dementia (Clinical Dementia Rating = 0.5 [22]), and 3 had previous diagnosis of another clinical psychiatric disorder. All but 2 had hyperactive delirium.

Medication Dosing

Mean maximum daily doses of regularly scheduled loxapine, PRN loxapine, and cumulative loxapine (regular +PRN) were 28mg (s.d. 23; range 0-100mg), 21mg (s.d. 21; range 0-80mg), and 44mg (s.d. 31; range 7.5-140mg) respectively.

Eight participants received methotrimeprazine (mean maximum daily dose = 10mg) and 7 received lorazepam (mean maximum daily dose = 2mg) at some point during their delirium. Fluoxetine, venlafaxine, haloperidol, clonazepam, oxazepam, carbamazepine, and gabapentin were each received at some point by a single participant.

DRS-R-98 Scoring

Mean DRS-R-98 score at diagnosis was 18.68 (s.d. 4.66; range 10-28). After two days of loxapine, the mean had fallen to 10.19 (s.d. 6.61; range 5-27). The mean change from day 0 to day 2 was -8.48 (s.d. 7.11; range -18-15; [$t(30) = 6.65$, $p < 0.001$]; see Figure **1**). The 3 participants who worsened from day 0 to day 2 improved from day 2 to day 4. Mean days to resolution of delirium (DRS < 10) was 3.2 (s.d. 2.5, range 2-14) with 68% resolving by day 2, 84% by day 4, and 90% by day 6.

Monitoring for Adverse Effects

EPS were absent in all but three participants who had mild Parkinsonism (subscale scores of 4, 5, and 7). There was no significant difference between baseline

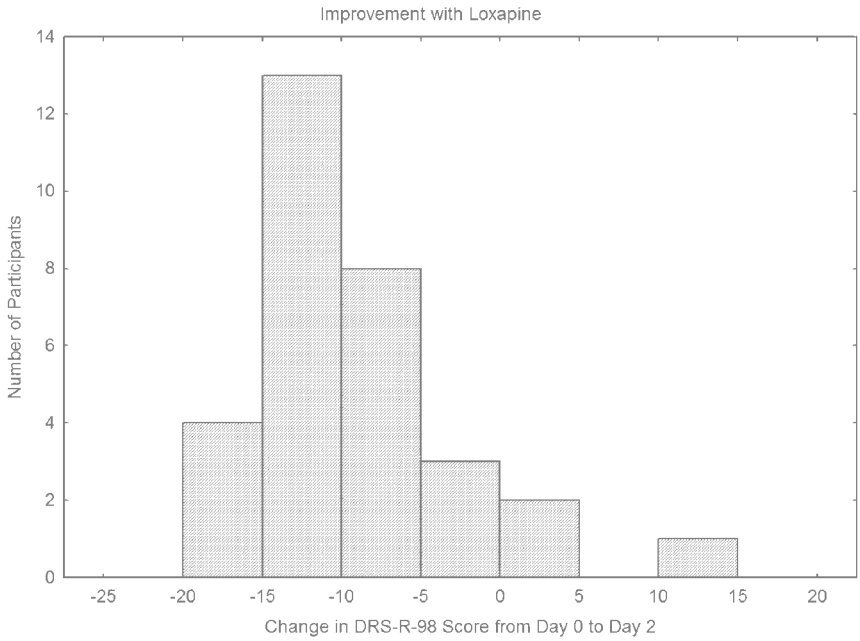

Figure 1: Improvement with Loxapine: The X-axis shows change on the DRS-R-98 from the time of diagnosis to 2 days after diagnosis. The Y-axis shows the number of participants that fall into each 5-point bin on the X-axis.

QTc (mean 422ms, s.d. 19.86) and mean QTc during treatment (mean 426ms, s.d. 18.47) in the subsample of 12 participants for whom QTc data for both time points were available [$t(11) = 0.45$, $p > 0.5$]. The mean change in QTc was 3.33 (s.d. 25.74, range -49.70 to 49.30), and there was not a significant correlation between maximum total dose and QTc change (see Table **1**). No falls or adverse cardiac events were recorded. One participant, a woman with acute myeloid leukemia, died during her hospitalization.

Table 1: QTc Data – This table shows QTc from a single 12-lead ECG performed before any loxapine was received and mean QTc from any 12-lead ECGs done during loxapine treatment for each participant who had both measures available

Participant	QTc Before Loxapine	QTc With Loxapine
1	415	438
2	407	456
3	409	398
4	431	411
5	421	429
6	427	446
7	468	447
8	401	421
9	413	423
10	407	411
11	452	402
12	417	426

DISCUSSION

The rapid improvement in DRS-98-R score is similar to findings with other medications in samples that included older post-operative patients [16,23] and suggests loxapine is an effective alternative. In addition, we did not observe significant EPS, unexpected adverse events, or increased QTc.

Sleep-wake cycle disturbance is present in 97% of patients with delirium and is often an early sign [24], suggesting it may lead to progression of severity. Finding that delirious patients spend less time resting at night, Jacobson *et al*. [25] proposed that delirium is a state of “pathological wakefulness”. Using wrist actigraphy, they demonstrated that delirious patients spend less time resting at night, less time resting over 24-hours, and more time moving at night. They also showed decreased change in activity level between day and night. In support of their theory, they point to similarities in EEG activity between delirium and sleep [26] and alterations in clock gene expression post-operatively [27]. Promoting restoration of a normal sleep-wake cycle has long been a cornerstone of non-pharmacologic interventions [15] and Al-Aama *et al*.’s [28] finding that nightly melatonin is effective in reducing incidence of delirium suggests preventative pharmacological measures targeting sleep may also be useful. Promoting nighttime sleep may be worth sacrificing some dopamine blockade and incurring slightly more anticholinergic burden in some patients.

In the United States, loxapine is available as an orally inhaled powder, administered via a single-use drug delivery system (ADASUVE™ and STACCATO™, respectively, both Alexza® Pharmaceuticals, Inc., California, United States). It is indicated for the rapid treatment of agitation in patients with schizophrenia or bipolar I disorder [29]. A major warning published by the Food and Drug Administration [29] regarding the use of inhaled loxapine, however, is that it causes bronchospasm and can lead to respiratory distress and arrest; thus, it is currently only available in the United States through the Risk Evaluation and Mitigation Strategy (REMS) program. But given the non-invasive route of delivery, plus its rapid onset, there may be a potential role for aerosolized or nebulized formulations of antipsychotics known to be effective for the treatment of delirium, particularly in the perioperative setting.

There are a number of limitations to this pilot study. This was a small, open-label study without a placebo control or a comparison medication with other psychotropic medications used in some patients. Because of a lack of placebo, it is possible the course of delirium would have been short in these patients even without loxapine. However, in studies that have included placebo control, delirium has persisted beyond the first few days in the placebo group [23,30]. Another limitation is the QTc data only being available for a subset of participants, though there is other evidence of safety [18,31-32]. Therefore, while this study does provide evidence that loxapine is a good medication to use in this population and suggests that further investigation of its use for delirium is warranted, caution should be taken in interpreting the findings.

CONCLUSION

Delirium is a common sequela of medical derangements, and is associated with significant outcomes for patients as well as for the healthcare system at large. Despite having a number of clinical monitoring tools and risk factor algorithms for delirium, the incidence remains high, and the choice of antipsychotic for treatment of delirium often depends on the clinician's familiarity and the drug's availability at the institution. Loxapine, an antipsychotic with mid-range potency, is both effective and efficacious at treating delirium and should be considered an option, especially given these initial findings on its QTc-preserving effects.

AUTHOR CONTRIBUTIONS

Drs. Bates, Chan, D'Oyley and Hewko designed and performed the study. Dr. Bates and Lurdes Tse wrote the manuscript, and this was also reviewed by Drs. Chan, D'Oyley and Hewko.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was approved by the UBC Providence Health Care Research Ethics Board.

INFORMED CONSENT STATEMENT

Informed written consent was obtained from patients or their substitute decision makers.

CONFLICT OF INTEREST STATEMENT

None of the authors declare any conflict of interest in this study.

DATA SHARING STATEMENT

The anonymized dataset is available from the first author. Loxapine for management of delirium in older adult surgical patients.

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Received on 05-06-2017 Accepted on 23-06-2017 Published on 05-07-2017

DOI: https://doi.org/10.12970/2310-8231.2017.05.05