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Evaluation of intramuscular olanzapine and ziprasidone in the medically ill

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Abstract

Introduction: Despite the paucity of studies evaluating short-acting parenteral second-generation antipsychotics in the medically ill, their use in this population has increased. The purpose of this study was to characterize the use of IM olanzapine and ziprasidone in the medically ill at an academic medical center.

Methods: This is a retrospective medical record review of all patients who received IM olanzapine or ziprasidone on nonpsychiatric inpatient units at a large academic medical center from August 1, 2015 to July 31, 2017. The primary endpoint characterized the indication for use. Secondary endpoints included safety, effectiveness, and prescribing patterns.

Results: After exclusion criteria, a total of 100 patients were included in this study, predominantly white males with a mean age of 56 years. Seventy-four percent of patients received IM ziprasidone and 26% received IM olanzapine. The most common indications for use were agitation of nonpsychotic origin (40%) and delirium (33%). Patients received IM olanzapine and ziprasidone when their use was contraindicated (26.9% vs 9.5%, respectively).

Discussion: Intramuscular second-generation antipsychotics are increasingly being used in the medically ill for delirium and agitation. Our study confirms these were the most common indications for IM second-generation antipsychotic use in this population. Additionally, their use appeared to be well-tolerated, and no patient developed Torsades de Pointes even when combined with other agents that putatively increase QTc. Given the retrospective, single-center, nonrandomized design of this study, the safety and effectiveness of these parenteral second-generation antipsychotics in common causes of acute agitation should continue to be further evaluated.

Keywords: agitation, intramuscular, olanzapine, ziprasidone, medically ill

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Introduction

Short-acting IM antipsychotics are frequently used to treat acute agitation. Haloperidol has been the most widely used parenteral antipsychotic in the medically ill to treat

acute agitation, however it is associated with extrapyramidal symptoms and a warning for corrected QT interval (QTc) prolongation with IV use.[1] The previously published 2013 Society for Critical Care Medicine (SCCM) guidelines[2] assert there is no supporting use of haloperidol for reducing delirium duration in adult intensive care unit patients and instead suggest that oral quetiapine may reduce the duration of delirium. The guidelines[2] also recommend against using antipsychotics in patients at significant risk for Torsades de Pointes, including those with a baseline prolonged QTc or being administered concomitant QTc prolonging medications. Second-generation antipsychotics (SGAs) are less likely to cause extrapyramidal symptoms than first-generation antipsychotics, but SGAs may still prolong the QTc interval.[2,3] Despite not having an approved indication outside of agitation related to schizophrenia or bipolar disorder, short-acting IM SGAs are increasingly being used in hospitalized medically ill patients.[4,5] Available literature evaluating the use of IM SGAs in treating agitation in the medically ill is limited and includes an open-label study that examined the safety and efficacy of IM ziprasidone with geriatric patients experiencing psychosis and agitation (N = 14), a retrospective study of the safety of IM ziprasidone in agitated hospitalized elderly patients (N = 23), a retrospective case series of hospitalized patients who received IM olanzapine outside product doses and indications (N = 10), and a retrospective study of IM olanzapine in the management of behavioral and psychological symptoms in hospitalized older adults (N = 85), however only 34 patients actually received the IM olanzapine.[6-9]

Two currently available short-acting IM SGAs are olanzapine and ziprasidone. Approval trials excluded medically ill patients and recent substance abuse.[10-14] Key safety parameters that apply across patient populations include maximum daily dose,[4,5] duration of use, avoiding IM ziprasidone in patients with a recent history of myocardial infarction or unstable heart disease, and avoiding parenteral benzodiazepine use within 1 hour of IM olanzapine.[10-14] IM olanzapine should not be given within 1 hour of parenteral benzodiazepines because of the risk of over-sedation, cardiorespiratory depression, and hypotension.[15,16] IM ziprasidone contains the cyclodextrin, a renally cleared excipient; therefore, should be used cautiously in renal impairment.[4] Overall, many factors in the pivotal studies for IM ziprasidone and IM olanzapine make it difficult to extrapolate the results to patients with medical illnesses who may be receiving doses beyond maximum recommended daily dose and studied duration.

Because of the limited literature of IM olanzapine and ziprasidone in medically ill patients, the objective of this retrospective review is to characterize the use and safety of these SGAs in the medical-surgical inpatient population at an academic medical center.

Methods

This study was a retrospective medical record review of patients who received short-acting parenteral olanzapine or ziprasidone on nonpsychiatric units at a large academic medical center licensed for 790 beds, with an average daily census of 592, from August 1, 2015 to July 31, 2017. The Virginia Commonwealth University IRB approved this study. Potential patients were identified via a pharmacy medical record report of all charted doses of parenteral olanzapine or ziprasidone on nonpsychiatric units. The intention was to capture patients who received IM or IV SGAs. No patients received IV, therefore IM will be used throughout the rest of this publication. Patients were included if they were at least 18 years of age, admitted to a nonpsychiatric unit, and received parenteral short-acting olanzapine or ziprasidone. Exclusion criteria included patients who received IM olanzapine or ziprasidone only in the emergency department, upon transfer to a psychiatric unit, prisoners, and pregnant women. The primary endpoint was indication for use of IM olanzapine or ziprasidone. Baseline comorbidities of schizophrenia, bipolar disorder, schizoaffective disorder, substance use history, and dementia were collected to determine on-label and off-label prescribing.

Secondary endpoints included safety, effectiveness, and prescribing patterns of IM olanzapine and ziprasidone. Safety of IM olanzapine and ziprasidone was assessed by adverse effects (hypotension, sedation, and falls), change in QTc interval, mortality, and prescribing when contraindicated. Adverse effect data was obtained from reviewing the medical record nursing notes, vital sign records, and Richmond Agitation-Sedation Scale (RASS) score.[17] Rates of adverse effects with each agent were compared. Presence of concomitant medication(s) with known, possible, or conditional risk of prolonging the QTc, as defined by CredibleMeds[18] were recorded. Effectiveness was assessed by the RASS,[17] a validated scale ranging from +4 (combative) to −5 (unarousable). The RASS score was chosen as an objective measurement that is collected on the majority of intensive care unit and medically ill patients. Improvement was defined as a reduction in a positive score to 0 or −1 (alert and calm or drowsy) within 1 hour of the first IM olanzapine or ziprasidone dose. Lack of improvement was documented if RASS score was unchanged or increased within 1 hour of the first IM olanzapine or ziprasidone dose. Sedation was documented if RASS score was reduced to −2 or −3 (light sedation or moderate sedation) within 1 hour of each administration of IM olanzapine or ziprasidone. Prescribing patterns of IM olanzapine and ziprasidone in the medically ill were compared based on select baseline characteristics or comorbidities including age, presence of diabetes, hyperlipidemia, recent myocardial infarction, prolonged QTc, uncompensated heart failure, or renal impairment (creatinine clearance <50 mL/min). These

TABLE 1: Summary of baseline characteristics and intramuscular olanzapine or ziprasidone administration

Patient Characteristics	N = 100
Age (y), mean ± SD	56 ± 17.5
Male, %	70
Ethnicity, %	
White	62
African-American	36
Hispanic	2
Baseline QTc on admission (msec), median	462 (n = 86)
Comorbid severe mental illness,[a] %	17
History of substance abuse, %	35
History of dementia, %	13
NPO status, %	34
Psychiatry consult, %	38
Received IM ziprasidone, %	74
Received IM olanzapine, %	26
Received a parenteral FGA prior to an IM SGA, %	40
Received the IM SGA in an ICU, %	64
Received IM SGA beyond studied duration, n (% of treatment arm)	
Olanzapine	6 (23.08)
Ziprasidone	10 (13.51)
Received IM SGA when use was contraindicated, n (% of treatment arm)	
Olanzapine	7 (26.9)
Ziprasidone	7 (9.5)

FGA = first-generation antipsychotic; msec = milliseconds; NPO = unable to take medications by mouth; QTc = corrected QT interval; SGA = second-generation antipsychotic.

[a]Severe mental illness was defined as schizophrenia (n = 8), schizoaffective disorder (n = 7), or bipolar disorder (n = 2).

TABLE 2: Intramuscular second-generation antipsychotic indication for use and characteristics

Indication	N = 100
On-label, %	5
Off-label, %	95
Psychiatric disorder,[a] %	8
Agitation of non-psychotic origin,[b] %	40
Delirium, %	33
Dementia-related agitation, %	4
Other,[c] %	11
Unknown	4
Characteristics	
Median total dosage in 24 h, mg (range)	
Olanzapine	6.3 (2.5-20)
Ziprasidone	20 (20-40)
Duration of use, d (median)	
Olanzapine	1-4 (1)
Ziprasidone	1-17 (1)
Median total cumulative dose received, mg (range)	
Olanzapine	8.8 (2.5-60)
Ziprasidone	20 (10-210)

[a]Schizophrenia (n = 5), schizoaffective disorder (n = 2), bipolar disorder (n = 1).

[b]Traumatic brain injury (n = 13); alcohol withdrawal syndrome (n = 9); substance abuse (n = 4); post-ischemic stroke (n = 3); hepatic encephalopathy (n = 3); seizures (n = 2); anti-N-methyl-d-aspartate encephalitis (n = 1); severe intellectual disability (n = 1); cerebral amyloid angiopathy related to inflammation (n = 1); hyponatremia (n = 1); dexamethasone (n = 1); levetiracetam (n = 1).

[c]Central line procedure (n = 3); mixed etiology (n = 4); infection (n = 2); used for sedation (n = 1); altered mental status due to hypercapnia (n = 1).

comorbidities were selected based on the exclusion criteria of pivotal trials, common adverse effects, as well as cautions and contraindications for each agent.

Statistical analyses were performed using JMP Pro Software version 13 (SAS Institute), with descriptive statistics for demographics and the primary endpoint. The χ^2 test was used to make comparisons between parenteral olanzapine and ziprasidone on secondary endpoints.

Results

Of the 138 total patients who received IM olanzapine or ziprasidone during the study period at a large academic medical center, 100 patients were included. Reasons for exclusion included patients on an inpatient psychiatric unit (n = 17), patients who received an antipsychotic only in the emergency department (n = 15), and patients who were less than 18 years of age (n = 6). Majority of patients were male (70%) and the mean age was 56 years (see Table 1). When evaluating patient characteristics, majority of patients (74%) received ziprasidone. The study institution uses both SGAs; however, at the time of data collection, IM ziprasidone was on formulary, whereas short-acting IM olanzapine was available for restricted use. Secondary to the risk of inadvertently combining IM olanzapine with parenteral benzodiazepines, short-acting IM olanzapine was restricted to inpatient adult psychiatry, child/adolescent psychiatry, and consult and liaison psychiatry; primarily for patients already on oral olanzapine or had a contraindication or adverse reaction to IM ziprasidone or IM haloperidol. A psychiatry consult was obtained in 38 patients, often after the IM SGA was administered. The most common indication for use of IM olanzapine or ziprasidone was agitation of nonpsychotic origin (40%), followed by delirium (33%; Table 2).

A total of 6 (23.08%) patients who received IM olanzapine were given the medication beyond the studied duration of 24 hours. A total of 10 (13.51%) patients who received IM ziprasidone were given the medication beyond the studied duration of 3 days. The most common adverse effect for

TABLE 3: Comparison of prescribing patterns of IM olanzapine versus IM ziprasidone

Baseline Medical History, n (%)	Olanzapine (n = 26)	Ziprasidone (n = 74)	*P* Value[a]
Diabetes	6 (23.08)	20 (27.03)	.69
Age ≥65 y	7 (26.92)	19 (25.68)	.90
Hyperlipidemia	1 (3.85)	6 (8.11)	.46
Recent myocardial infarction	3 (11.54)	2 (2.70)	.075
QTc interval ≥450 msec[b]	15 (60)	36 (59.2)	.93
QTc interval ≥500 msec[b]	6 (24)	9 (14.8)	.30
Uncompensated heart failure	1 (3.85)	5 (6.76)	.59
Renal impairment (CrCl <50 mL/min)	9 (34.62)	13 (17.57)	.071

CrCl = creatinine clearance; msec = milliseconds; QTc = corrected QT interval.

[a]χ^2 test.

[b]Percent cacluated based on electrocardiograms obtained olanzapine n = 25, ziprasidone n = 61.

patients who received IM olanzapine or IM ziprasidone was sedation. There was no significant difference in rates of sedation between IM olanzapine or IM ziprasidone (34.62% vs 24.32%; *P* = .32), respectively. Significantly more patients who received IM olanzapine had hypotension compared to those who received IM ziprasidone (23.08% vs 6.76%; *P* = .022). Falls occurred at similar rates in both IM olanzapine (7.7%) and IM ziprasidone (8.1%). No patients died.

Of the patients who had a baseline QTc (Bazett's correction formula) on admission (n = 86), the mean QTc was 462 milliseconds (msec). Patients who received IM olanzapine had a higher baseline QTc than the ziprasidone group (473.2 msec vs 464.9 msec, respectively). Only 57 patients had a follow-up electrocardiogram after their last dose, 34.6% (n = 19) of olanzapine versus 51.4% (n = 38) of ziprasidone patients. Approximately 42.1% (n = 8) of olanzapine and 34.2 % (n = 13) of ziprasidone patients experienced an increase in their QTc inteval. The median (interquartile range) change in QTc from baseline for IM olanzapine 36.5 (5.3-52.3) msec and 16 (10-42.5) msec in patients who received IM ziprasidone. Additionally, the majority of patients (71%) had received concomitant medication(s) with known, possible, or conditional risk of prolonging the QTc, as defined by CredibleMeds (this was equally true for both medications).[19] Oral antipsychotics were the most commonly coprescribed QTc prolonging agents that were received: haloperidol (n = 44), quetiapine (n = 37), olanzapine (n = 6), risperidone (n = 3) lurasidone (n = 1), ziprasidone (n = 1), and trifluoperazine (n = 1). Other QTc prolonging psychotropic agents coprescribed and received were citalopram (n = 1), lithium (n = 1), nortriptyline (n = 1), and sertraline (n = 1).[18] Thirty-three (33%) patients received 2 or more additional QTc prolonging agents, with 1 patient receiving 4 QTc prolonging agents in addition to ziprasidone. Given the limitations of using CredibleMeds and the inconclusive effects of some of these medications on the QTc (eg, sertraline, lithium), no conclusions or associations can be made between the concomitant medications used and their effect on QTc interval. Of those who had a RASS score documented after the first dose, improvement was seen in 11 (42.31%) patients who received IM olanzapine and 30 (40.54%) patients who received IM ziprasidone. However, this was not documented in over half of the patients after receiving the first dose of IM olanzapine or IM ziprasidone (57.79% vs 55.41%). Lack of improvement was documented in 0% and 4.05% after IM olanzapine and IM ziprasidone, respectively.

There were no statistically significant differences in prescribing patterns based on baseline medical history between patients who received IM olanzapine vs those who received IM ziprasidone. Seven patients received IM ziprasidone when it was contraindicated, 2 who had a recent myocardial infarction and 5 who had uncompensated heart failure (Table 3). Seven patients who received IM olanzapine were given a parenteral benzodiazepine within 1 hour of administration.

Discussion

In this retrospective medical record review of 100 medically ill patients who received IM olanzapine or ziprasidone at an academic medical center, the most common indication for use was agitation of nonpsychotic origin (40%), followed by delirium (33%). This supports the clinical experience that these agents are increasingly being used for these indications. Two published cases of sudden and unexpected deaths in patients with schizophrenia who received high doses of IM haloperidol and IM ziprasidone led to practice guidelines to limit the use of high doses of IM antipsychotics.[19] In this study, no patient received more than the maximum recommended total daily IM dose of either antipsychotic. One patient received

50 mg of ziprasidone in IM equivalents, with IM and oral route combined (IM = 20 mg + oral = 120 mg [30 mg in IM equivalents]).

Despite a prolonged baseline QTc or concurrent QTc prolonging medications many patients still received IM ziprasidone; however, similar to Greco et al[7] none of these cases resulted in Torsades de Pointes. The high rates of concomitant quetiapine reflect its recommendation for agitation in the 2013 SCCM guidelines,[2] as well as the high rates of haloperidol reflect its historical use for agitation in this population. Since completion of our study, SCCM published an updated 2018 guideline[20] which again discourages *routine* use of haloperidol or antipsychotics to treat delirium. However, they suggest patients who experience significant distress or agitation and may be at harm to themselves or others may benefit from short-term use of an SGA or haloperidol.[20] Clinical pharmacists in the intensive care unit setting can help reduce the number of patients who remain on these agents after symptom resolution or discharge. The greater change in QTc from baseline in patients who received IM olanzapine may be explained by the higher baseline QTc in this group and possibly by prescribers selectively choosing IM olanzapine over ziprasidone for these patients judged to be at higher risk for QTc prolongation. Patients with baseline prolonged QTc may also have had other risk factors for QTc prolongation, which were not accounted for. Therefore it is difficult to draw conclusions regarding change in QTc in this population. Futhermore, the medically ill population may be on multiple other antihypertensives or experience dehydration, which also was not accounted for. Our study found rates of hypotension significantly higher with IM olanzapine (23.08%) than IM ziprasidone (6.76%); similarly the previous studies regarding IM olanzapine also had high rates of orthostatic hypotension (12.5% and 14.7%).[8,9] Doung et al[9] reported falls in 4 of 34 (11.8%) elderly patients within 24 hours of receipt of IM olanzapine, a rate higher than the approximate 8% described in our study. This may also be reflective of the younger average age of our population. This is the largest study to date retrospectively evaluating the use of IM SGAs in the medically ill on nonpyschiatric units at an academic medical center. Most previous data have primarily been in elderly patients, primarily with dementia, and this study included younger medically ill adults. The previous IM ziprasidone studies[6,7] focused on older adults on psychiatric or neuropsychiatric units, whereas in the IM olanzapine studies,[8,9] 50% or greater of the population was on inpatient psychiatry. Of the previous literature, Lamoure and Rudnick[9] looked at the off-label uses of IM olanzapine in 8 patients (average age 43.9 [range 18-77]) across 10 admissions which included patients on a surgery floor (n = 4) and internal medicine (n = 1). Fifty percent of patient encounters had concurrent alcohol or substance withdrawal or intoxication, and 2 had a TBI. Our study adds to the limited safety data of using these agents in the medically ill with concurent substance abuse or intoxiciation.

However, there are several limitations to this study including a restrospective, single-center study design, small sample size, a relatively high percentage of patients who received a parenteral first-generation antipsychotic prior to receiving the IM SGA, and incomplete documentation in the electronic medical record. Additionally, the low number of patients who received IM olanzapine may be accounted for by the nonformulary status of this medication at this institution. There may have been other confounding variables that could have caused the adverse effects noted, so it is difficult to correlate these adverse effects directly with the IM SGA administered. Evaluating for improvement in RASS score was only performed after the first dose. Therefore, it is possible that improvement after further doses could have occurred. Furthermore, the exact change from baseline in RASS score to evaluate for effectiveness was not documented. A total of 7 patients received parenteral benzodiazepines within 1 hour of IM olanzapine administration. None of these patients experienced any adverse effects. Marder et al[15] advised caution when using IM olanzapine and parenteral benzodiazepines concomittantly after observing 29 fatal cases of IM olanzapine, of which 15 (51.7%) reported concomitant oral, IV, or IM benzodiazepine use. The lack of adverse effects seen with this combination in our study may be due to limitations in documentation and the small number of patients receiving this combination.

Since the completion of this study, our institution also completed a medication-use evaluation on short-acting IM olanzapine (in psychiatric patients) and it was ultimately added to formulary, without restrictions. A pharmacy-specific alert warns the verifying pharmacist to review the medication profile for parenteral benzodiazepines and suggest discontinuation. Additionally, the institutional product instructions for use state to not administer within 1 hour of a parenteral benzodiazepine.

Conclusion

This study characterizes the indications and clinical safety data of IM olanzapine and ziprasidone in the medically ill. IM SGAs are currently being used more often in the medically ill for delirium and agitation. Our findings confirm these were the most common indications for IM SGA use. This study also adds to the limited safety data of IM SGAs for these off-label indications. Our data supports the clinical experience that Torsades de Pointes did not occur even when combining IM SGAs with other agents that putatively increase QTc. Additional data is still

needed to continue to support and evaluate the safety and effectivess of parenteral SGAs in common causes of acute agitation in medically ill as well as compare their use to haloperidol in this population.

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