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Coadministration of intramuscular olanzapine and benzodiazepines in agitated patients with mental illness

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Abstract

Introduction: Intramuscular antipsychotics are commonly used to manage agitated patients. In 2005, Eli Lilly placed a warning on olanzapine's prescribing information following post-marketing reports of fatal drug reactions when intramuscular olanzapine was used in the setting of benzodiazepines. Data is lacking examining this drug combination.

Methods: A medication use evaluation was conducted at a county psychiatric hospital surveying the usage of concomitant intramuscular olanzapine and lorazepam from October 1, 2016, to July 20, 2017. A literature search was conducted to review available evidence.

Results: Ninety-one instances of the drug combination were discovered, with no serious adverse events following administration. Of these 91 patients, 41 received both medications within 60 minutes of each other. No instances of hypotension, bradycardia, bradypnea, or oxygen desaturation occurred following administration. The literature review yielded 1 randomized, placebo-controlled clinical trial, 3 retrospective chart reviews, and several case studies.

Discussion: Data detailing a causal relationship between olanzapine/benzodiazepine combinations and serious adverse effects is lacking. Available evidence does not consistently support a strong cause and effect relationship. The results of this medication use evaluation are not consistent with the Food and Drug Administration warning. Further controlled research is needed to help define the actual risk of using concomitant intramuscular olanzapine and benzodiazepines.

Keywords: intramuscular olanzapine, benzodiazepines, agitation

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Introduction

Agitation in the psychiatric setting is a common occurrence that is associated with a variety of psychiatric disorders. During extreme agitation episodes, after verbal de-escalation has failed, clinicians rely on the use of psychotropic medications to limit risk of harm to the patient or others.[1,2]

Antipsychotics have become the mainstay of pharmacological management of acute psychiatric agitation.[3,4] While many clinicians still rely on first generation antipsychotics such as haloperidol, fluphenazine, and chlorpromazine for acute agitation, the American Association of Emergency Psychiatry recommends the use of second generation antipsychotics (SGAs) as first-line agents.[5,6] Second generation antipsychotics have been shown to cause less extrapyramidal side effects than first generation antipsychotics, and appear to be as effective at controlling agitation.[7-9]

TABLE 1: Summary of instances (n = 91) of coadministration of intramuscular olanzapine (OLZ) and lorazepam (LZP) within a 24-hour period

	OLZ Dose, mg	LZP Dose, mg	Time Between Doses, min	Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	Pulse, beats/min	Respiratory Rate, breaths/min	Pulse Oximetry, %
Mean	9.84	1.88	160.11	123.66	74.98	88.28	18.58	97
Median	10	2	126	125	74	86	18	97
Minimum	5	1	0	90	53	57	16	96
Maximum	10	2	909	176	111	128	24	100

In potentially dangerous situations, intramuscular (IM) route of administration may be preferred by providers and nursing staff. Available IM antipsychotics used for agitation include haloperidol, chlorpromazine, fluphenazine, olanzapine, and ziprasidone. In 2015, aripiprazole's rapid-acting IM was discontinued, leaving olanzapine and ziprasidone as the only SGA options currently available.[10]

Despite a lack of compelling evidence, combinations of psychotropic medications are commonly used in practice to treat agitation. Combinations may include an antipsychotic, an anticholinergic agent, and/or a benzodiazepine. Rationale for combining an anticholinergic or benzodiazepine with the antipsychotic agent may be to mitigate potential extrapyramidal side effects, added calming effect, or to intensify the level of sedation.[4,11,12] Despite an absence of strong evidence supporting the safe use of parenteral olanzapine-benzodiazepine combination, it is used in psychiatric emergency departments.[13-16]

Because of the lack of information regarding the combination of IM SGAs and benzodiazepines, caution should be exercised if they are coadministered. Currently, IM olanzapine is the only SGA with a warning listed in its Food and Drug Administration (FDA) prescribing information stating, "concomitant administration of intramuscular olanzapine along with benzodiazepines is not recommended due to the potential for excessive sedation and cardiorespiratory depression."[17] This advisory is the result of 160 postmarketing adverse events, including 29 fatalities, associated with IM olanzapine published in 2005.[13]

Olanzapine is classified as a thienobenzodiazepine, with a very similar chemical structure to that of lorazepam. It is considered to be highly sedating in comparison to other SGAs.[18] It also demonstrates alpha-1 receptor antagonism, which may contribute to hypotension. When administered intramuscularly, its maximum concentration is 5 times higher than a maximum concentration following oral administration.[17] When coupled with an IM benzodiazepine, the likelihood for sedation and possible cardiorespiratory depression may be increased, especially given the similarities in chemical structures of both agents.[17,19] Therefore, the European Medicines Agency recommends separating the administration of IM olanzapine and IM benzodiazepines by at least 60 minutes.[20] The FDA does not have a specific recommendation regarding separation of the 2 medications, but rather just warns against coadministration in general. As a result of this warning, many medical centers have opted to avoid the combination in management of agitated patients.[14]

A Medication Use Evaluation (MUE) was conducted at a county medical center with 77 licensed inpatient psychiatric beds and over 8000 psychiatric emergency patient encounters per year. Currently, this institution does not have a policy and procedure in place regarding the coadministration of IM olanzapine and benzodiazepines. At this institution, nursing staff is able to obtain certain medications (antipsychotics, benzodiazepines, antihistamines) from the dispensing cabinets for psychiatric emergencies without pharmacist approval.

TABLE 2: Summary of instances (n = 41) of coadministration of intramuscular olanzapine (OLZ) and lorazepam (LZP) within a 60-minute period

	OLZ Dose, mg	LZP Dose, mg	Time Between Doses, min	Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	Pulse, beats/min	Respiratory Rate, breaths/min	Pulse Oximetry, %
Mean	9.76	1.8	5.31	121.59	72.85	86.92	18.44	97.56
Median	10	2	1	121	73	81	18	97
Minimum	5	1	0	90	53	62	16	96
Maximum	10	2	57	147	94	117	22	100

TABLE 3: Evidence of using parenteral olanzapine with benzodiazepines

Study (y)	Study Characteristics	Intervention	Findings
Marder et al[13] (2010)	Study design: case series Setting: various inpatient settings worldwide Patient population: various diagnoses, average age 49.1 y old	Searched the Eli Lilly-maintained safety database for adverse events associated with IM olanzapine	160 Cases containing adverse events were reported, including 29 fatalities following IM olanzapine injections Benzodiazepines (oral or injection) were associated in 83% of fatal cases –Administered in 7/9 fatal case reports of elderly patients Time of death following olanzapine injection ranged from 30 min to 18 d post-dose
Chan et al[21] (2013)	Study design: randomized, double-blind, placebo-controlled, double-dummy, clinical trial Setting: 3 emergency departments in Australia Patient population: Acutely agitated adults n = 336 (control group: 115, droperidol group: 112, olanzapine group: 109)	Agitated patients were randomized to receive initial intravenous bolus of saline (control), droperidol 5 mg, or olanzapine 5 mg. Boluses of midazolam 2.5 mg to 5 mg were given until sedation was achieved.	Time to achieve adequate sedation was significantly lower in droperidol (4 min shorter) and olanzapine (5 min shorter) groups compared to placebo Patients who experienced any adverse events (%): –Control: 18 (15.7) –Droperidol: 12 (10.7) –Olanzapine: 9 (8.3) Of note, was not sufficiently powered to compare safety
Wilson et al[15] (2012)	Study design: retrospective chart review Setting: 2 emergency departments in Southern California Patient population: Adults with undifferentiated agitation n = 25 (olanzapine and benzodiazepine: 10, olanzapine only: 15)	Inclusion criteria: received IM olanzapine and contained documentation of vital signs and oxygen saturation before and after olanzapine administration Average doses: –Olanzapine IM monotherapy: 10 mg –Olanzapine IM + lorazepam equivalent: 11.5 mg + 1.9 mg, respectively	Oxygen saturations were lower in the olanzapine + benzodiazepine group: 95.7% ± 4.6% vs 98.5% ≤ 1.6% in olanzapine-only group following injection Average drop in oxygen saturation from baseline was larger in combination group vs monotherapy (2.4% vs −0.2%, $P = .045$) Increasing EtOH levels were significantly associated with drops in oxygen saturation (b = 0.5, $P = .03$) No difference in oxygen saturation between monotherapy and combination therapy in patients with no EtOH use ($P > .4$) No difference in heart rate or respiratory rate following injection in both groups ($P > .4$, $P > .5$, respectively)

Methods

A report was generated detailing all patients who received IM olanzapine and IM lorazepam at any time during their admission between October 1, 2016, and July 20, 2017. The patient list was retroactively evaluated by the clinical pharmacist, and patients who received both IM olanzapine and IM lorazepam within a 24-hour period were included for further investigation. A 24-hour administration window was selected in an attempt to mirror the clinical scenarios reported in the Marder article[13] presenting 29 post-marketing fatalities. The incidences of coadministra-

TABLE 3: Evidence of using parenteral olanzapine with benzodiazepines (continued)

Study (y)	Study Characteristics	Intervention	Findings
Wilson et al[16] (2012)	Study design: retrospective chart review Setting: 2 emergency departments in Southern California Patient population: Adults with undifferentiated agitation n = 96 patients (25 olanzapine patients from previous study, haloperidol + benzodiazepine: 39, haloperidol: 32)	Patients who received parenteral haloperidol and contained documentation of vital signs and oxygen saturation before and 4 hours after administration Data was compared to olanzapine data from previous study	Decreases in blood pressure were larger in patients who received haloperidol + benzodiazepines compared to olanzapine + benzodiazepine Decreases in oxygen saturation did not differ between haloperidol + benzodiazepine vs olanzapine + benzodiazepine when patients were EtOH negative
Zacher et al[19] (2005)	Study design: case report Patient: 46-y-old African American male with paranoid schizophrenia	Patient received IM olanzapine 10 mg and then IM lorazepam 2 mg, 30 min later	Patient's blood pressure prior to medications: 124/74 mm Hg Patient's blood pressure 6 hours following injections: 66/30 mm Hg Patient received 5 more IM olanzapine injections following incident without adverse reaction –Total of 19 olanzapine IM doses over a 10-d period

EtOH = ethanol/alcohol; IM = intramuscular.

tion of both medications within 60 minutes were then sub-analyzed.

Vital signs were collected from the electronic health record for patients found to have received both medications within the defined temporal window. Vital signs collected include: blood pressure, pulse, respiratory rate, and pulse oximetry (not available for every patient). The vital signs recorded for the MUE were the ones closest to the administration of the second IM injection within the 24-hour window. Hypotension was defined as a systolic blood pressure less than 90 mm Hg. Bradycardia was defined as less than 60 beats per minute. Bradypnea was defined as less than 12 breaths per minute. Oxygen desaturation was defined as an oxygen saturation less than 95%.

A PubMed literature search was also conducted to identify any published studies examining the coadministration of IM or intravenous (IV) olanzapine and benzodiazepines. Search terms included: *olanzapine AND lorazepam*, *olanzapine AND midazolam*, *olanzapine AND diazepam*, *olanzapine AND chlordiazepoxide*, and *olanzapine AND benzodiazepine*. Inclusion criteria was defined as: clinical trials, retrospective studies, or case reports specifically describing coadministration of parenteral olanzapine and benzodiazepines, written in English. There was no defined date range for inclusion. The search was completed on July 25, 2017, and included all dates of publication.

Appropriate internal review board approval was obtained from this institution in order to conduct this MUE and present these findings. Descriptive statistics are presented, and no statistical analysis occurred.

Results

Table 1 contains patient characteristics of the 91 instances of coadministration of IM olanzapine and lorazepam. Seven patients refused to have vital signs taken following administration; however, the nurse was able to document the observed respiratory rate. Pulse oximetry was collected in only 32 patients.

Table 2 summarizes patient characteristics of the 41 instances of coadministration within a 60-minute period. Similar to the 24-hour administration, there were no instances of hypotension, bradycardia, or bradypnea following the administration of IM olanzapine and lorazepam.

Table 3 contains available studies investigating the coadministration of olanzapine and benzodiazepines. Only

1 clinical trial exists, to date, evaluating the coadministration of IV olanzapine and benzodiazepines. Aside from this trial, one retrospective study and several case reports have been published investigating the coadministration of IM olanzapine and benzodiazepines.

Discussion

Following reports of 29 fatalities of patients who received IM olanzapine in the setting of benzodiazepines, a warning was placed on the prescribing information, cautioning providers from using this combination.[13] A closer look at the published reports reveals that 12 cases of death occurred >24 hours up to 12 days (n = 1) following the injections. This lapse in time frame makes it difficult to draw a strong *cause and effect* relationship. Furthermore, many of the cases (n = 14) in which death occurred described patients with very serious comorbid medical illnesses or following serious suicide attempts, which may have contributed to the fatalities. For example, 1 of the listed fatalities describes a successful suicide attempt 9 days after receiving the last olanzapine dose, which was counted as a combination-related fatality. Approximately 83% of reported fatalities were associated with benzodiazepines, which implies that benzodiazepine use may be a risk factor in fatal adverse events and led to the FDA warning cautioning against the use of concomitant use of IM olanzapine with benzodiazepines.[13] It is important to note that this figure was inclusive of all patients who received any form of benzodiazepine (oral, IM, or IV) at any point during the course of treatment when IM olanzapine injection was received.

Chan and colleagues[21] conducted the only randomized, double blind, placebo-controlled trial to date evaluating parenteral olanzapine and parenteral benzodiazepine coadministration. The study took place in Australia and their main objective was to evaluate time needed to achieve adequate sedation in patients receiving IV formulations of droperidol (n = 112) or olanzapine (n = 109), both in combination with midazolam.[21] In their findings, they also presented some initial safety data pertaining to adverse events. The olanzapine-midazolam combination was associated with the least number of patients (n = 9) experiencing adverse events compared to the control group (n = 18) and the droperidol-midazolam group (n = 12). Adverse events associated with the olanzapine-midazolam group included less airway obstruction (n = 3), oxygen desaturation (n = 5), and hypotension (n = 3). A major criticism to this study's findings, however, is that safety/tolerability was not a study objective. Additionally, droperidol is not routinely used in psychiatric hospitals in the United States, and many hospitals restrict the use of IV antipsychotics because of safety concerns. Furthermore, IV olanzapine is not FDA-approved for use in the United States. These differences in clinical practice weaken the external validity of the study.

A much smaller study by Wilson and colleagues[15] examined the combination, retrospectively reviewing data for patients (n = 10) who received a combination of IM olanzapine and IM lorazepam. Patients who received this combination had a greater decrease in oxygen saturation than patients who received olanzapine monotherapy, especially if they entered the emergency department intoxicated. A second study[16] was conducted by the same researchers in which data from the first study was compared to patients who received IM haloperidol in combination with a benzodiazepine (n = 39) within the same time frame. This comparison found that marginally significant blood pressure decreases were more pronounced in the haloperidol + benzodiazepine group compared to olanzapine + benzodiazepine recipients ($P = .06$). Interestingly, there was no difference in oxygen saturation rates between the 2 groups for patients with no alcohol in their systems. These findings suggest that coadministration of IM benzodiazepines with antipsychotics other than olanzapine may also pose a risk of hypotension and oxygen desaturation, especially when patients are intoxicated. It may be a set of adverse events that are associated only with the benzodiazepines, independent of the antipsychotic that is coadministered. A limitation of the studies is that it is difficult to make a definitive recommendation from this data because of the small size of the study population and retrospective study design.

This MUE is not intended to be a scientific study; however, given the large number of instances uncovered, it would be of benefit to further investigate this combination in this institution's patient population. In all instances the combination was tolerated without major adverse drug reactions. There were no instances of hypotension, bradycardia, or bradypnea following the administration of IM olanzapine and lorazepam. There were some deviations in pulse rate, including several instances of tachycardia, which may be expected when a patient is acutely agitated or receiving muscarinic receptor antagonist medications. Of note, the patients included in this MUE received additional medications other than olanzapine and lorazepam. Similar to real world practice, these patients received various doses of other psychotropic medications, as well as several different injections of rapid-acting antipsychotics, benzodiazepines, and antihistamines. Additionally, patients with a court order for IM back up for refusal of oral medications increased the risk of receiving multiple injections. This was particularly true for patients who received IM olanzapine and IM lorazepam >60 minutes apart from each other. Nearly every patient (n = 40/41) who received IM olanzapine and IM lorazepam

within 60 minutes of each other received the coadministration during a psychiatric code scenario.

The post-marketing case reports that led to olanzapine's regulatory warning regarding risk of cardiorespiratory depression when combined with benzodiazepines struggle to offer strong evidence of a causal relationship. Further studies failed to show a distinct causal relationship unique to IM olanzapine + benzodiazepine combination and these adverse events, although these studies contained their own limitations and weaknesses in study design. While an absolute contraindication of the combination may be a bit excessive, practitioners should always exercise caution when administering any parenteral medications to an agitated patient as there are always inherent risks with using this medication delivery method. Until more reliable safety data is available, clinical judgement should be exercised in using the IM olanzapine + lorazepam combination.

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