THE USE OF INTRAMUSCULAR BENZODIAZEPINES AND ANTIPSYCHOTIC AGENTS IN THE TREATMENT OF ACUTE AGITATION OR VIOLENCE IN THE EMERGENCY DEPARTMENT

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Abstract—The management of an agitated, abusive or violent patient is a common and challenging problem in Emergency Medicine. Priorities include measures to ensure the safety of the patient and the emergency staff, including provision of physical restraint of the patient and evaluation for correctable medical causes of such behavior. Medications used in the treatment of such patients include benzodiazepines and antipsychotic agents. The newer atypical antipsychotic agents seem to provide a safe and effective treatment for such patients. The atypical antipsychotic agents may have fewer short-term side effects than older typical antipsychotic agents, such as haloperidol and droperidol. Currently available atypical antipsychotic medications for the treatment of acute agitation include ziprasidone and olanzapine, which can be administered in an intramuscular formulation, and risperidone, which is available in a rapidly dissolvable tablet and liquid formulation. © 2006 Elsevier Inc.

Keywords—benzodiazepines; antipsychotic agents; acute agitation in the emergency department; psychosis; injectable atypical antipsychotic medications; psychiatry

INTRODUCTION

The management of the agitated or violent patient is a common and challenging problem in Emergency Medicine. As in much of emergency care, the emergency physician must frequently manage the difficult behavior while determining the etiology. Behaviors that can precede violence include excessive motor or verbal activity, apparent irritability, or vocal outbursts. Many times the patient is brought to the Emergency Department (ED) by police, medics, family or coworkers for evaluation and subsequent management of such behavior. The patient may, in fact, have been violent and brought to the ED in full restraints. In the ED, the patient must be protected from self-inflicted harm or inadvertent harm associated with physical restraint, such as aspiration or limb ischemia. The initial management of the agitated or violent patient modifies or even supercedes the doctor-patient relationship because the patient’s behavior must be controlled by physical restraint if necessary to ensure the safety of others (1). Given these challenges, a treatment approach that provides safe, rapid and effective intervention to control agitation, and aggressive or violent behavior is most desirable. When the undesirable side effects of treatment are minimized, the patient appreciates the calming effect induced and a therapeutic relationship between the physician and patient can be established.

In one recent study regarding the management of acutely agitated behavior, the recommended initial management strategies for the imminently violent patient included talking with the patient, offering food or drink,
offering oral medication, and displaying a show of force. If such measures are ineffective or not possible to implement, the second tier of approach involves the use of emergency medication with or without physical restraint (1).

The categories of emergency medication, typically given intramuscularly, for the immediate treatment of acute agitation or violent behavior include the benzodiazepines, conventional high potency antipsychotics (often termed “typical”) and, more recently, atypical antipsychotics. The specific agents used most frequently by intramuscular injection in the ED are a benzodiazepine, lorazepam (Ativan®), a conventional high potency antipsychotic, haloperidol (Haldol®), or one of the atypical antipsychotic medications such as: ziprasidone (Geodon®), and most recently olanzapine (Zyprexa®). Two atypical antipsychotics available in an oral disintegrating tablet are Risperidone (Risperdal®M-TAB™) and olanzapine (Zyprexa® Zydiss®). To use an oral tablet in any form there must be at least minimal cooperation by the patient. A conventional high potency antipsychotic, Droperidol (Inapsine®), was (and in some centers still is) a popular agent used to calm behavior in such patients; it was given in both intramuscular and intravenous doses.

Within the past several years, however, the Food and Drug Administration (FDA) has issued a black box warning regarding prolongation of QTc intervals, cardiac dysrhythmia and death in patients treated with droperidol; and droperidol is no longer routinely recommended for such patients.

The selection of an intramuscular medication depends, to some extent, on the cause of the agitation. Such causes generally fall into one (or more) of three major categories: a general medical condition, substance intoxication or withdrawal, or a primary psychiatric disturbance (usually schizophrenia or mania) (2). The categories form major branches of the decision tree shown in Figure 1.

The management of a patient with a general medical condition involves a medical assessment including vital signs, appropriate history, physical examination, and laboratory testing, as directed by the clinical assessment. This process is sometimes described as “medical clearance” (3). The specific treatment approach may directly treat a medical condition (such as giving some form of glucose to the hypoglycemic patient or lowering blood pressure in the patient with hypertensive encephalopathy). When nonspecific agents are used in such conditions, benzodiazepines,

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**Figure 1. Algorithm for the treatment of acute agitation in the ED.**

- Agitated Patient
- Focused Assessment (vitals/H&P)
- Medical Condition
  - Lab Tests as Determined by Physician
  - Treat Medical Condition (glucose for hypoglycemia, BP medication for hypertensive encephalopathy)
- Substance Abuse (withdrawal/intoxication)
  - Benzodiazepine (Lorazepam 0.5 - 2 mg IV/IM)
  - May Need Psychotropic Medications in Conjunction with Other Treatments
- Primary Psychiatric Disturbance
  - Attempt Discussion Regarding Behavior with Patient
  - Oral Medication
  - Show of Force

haloperidol, and more recently, ziprasidone or olanzapine are the agents of choice.

In the case of agitated violent behavior associated with acute withdrawal from alcohol, benzodiazepines or barbiturates are generally the preferred treatment. They may be used alone or in combination with primary psychiatric medications, depending on the patient’s circumstance. A recent meta-analysis of nine prospective controlled trials discussing the treatment of acute alcohol withdrawal demonstrated that “sedative-hypnotic agents are more effective then neuroleptic agents in reducing duration of delirium and mortality” (4). Statistically significant differences between various benzodiazepines and barbiturates were not found. In all cases reviewed, no cases of death were reported with the use of either benzodiazepines or barbiturates.

For all agents oral administration is preferred to an intramuscular injection if the patient accepts it. Currier and Simpson found that oral treatment with risperidone and lorazepam were as well tolerated and effective as intramuscular haloperidol and lorazepam for short-term treatment of acute agitation (5). Patients may improve quickly after the administration of an oral dose of medication, and this, in part, results from the patient’s feeling that their needs have been addressed (6). The acutely agitated patient is often unwilling or unable to take any oral medication, making intramuscular administration a necessary and essential alternative.

The goal of treatment for the emergency physician is to rapidly control agitated behavior and cause the fewest side effects possible. In addition, some consideration ought to be given as to which agent will be most easily switched to an oral form (7). An ideal medication would be used in both the acute and long-term setting, it would be well tolerated by the patient and therefore have a good compliance rate, and the change from parenteral to oral form would be relatively easy.

The patient and the physician will benefit from a drug that will calm the agitated patient without causing excessive sedation. This will allow the patient to rest while still participating in the treatment process and will enable the physician to obtain an appropriate history, initiate a work-up to identify etiologies of the patient’s agitation, and begin treatment. Excessive somnolence frequently hinders this evaluation process (8).

**BENZODIAZEPINES**

Lorazepam (Ativan®) is the most frequently used benzodiazepine for treatment of acute agitation. A 2-mg dose of intramuscular lorazepam has been found to be as effective in treating agitation and aggressive behavior as a 5-mg intramuscular dose of haloperidol (9). In contrast to some other benzodiazepines, it is rapidly absorbed after intramuscular injection. A dose of 0.5 to 2 mg every 1 to 6 h, administered intramuscularly, has a rapid onset of action and a relatively short duration of action (half-life 10 to 20 h). In contrast to haloperidol, lorazepam is associated with no extrapyramidal side effects or other neurological problems such as neuroleptic malignant syndrome (8,9). Risks associated with its use are usually minimal for a single dose or short-term administration (10).

Intramuscular midazolam (Versed®) also has been shown to reduce agitation. It is rapidly absorbed when administered intramuscularly. In a study evaluating the effectiveness of midazolam in treating agitation, 5 mg of intramuscular midazolam was superior to 10 mg of haloperidol (11). In a study comparing the use of intramuscular midazolam, haloperidol, and lorazepam in restraining violent and severely agitated patients, midazolam was found to more quickly control patients than lorazepam or haloperidol (12). Although acute onset of action is ideal, one potential drawback with midazolam may be its relatively short half-life. In healthy individuals, the elimination half-life is approximately 1.5–2.5 h. To adequately control the acutely agitated patient, a medication with a longer duration of action may be preferred to reduce the need for frequent re-dosing.

Benzodiazepines have been associated with excessive sedation and, less frequently, paradoxical disinhibition, which can pose a significant problem in the treatment of some agitated patients (10). Furthermore, excessive somnolence can be negatively viewed by the patient, and possibly deter them from seeking medical attention in the future. The potential abuse, dependence, and tolerance of these agents are some of the features that limit the usefulness of benzodiazepines to short-term use in the treatment of agitation.

**CONVENTIONAL ANTIPSYCHOTICS**

Intramuscular forms of a variety of neuroleptics are currently in use. Haloperidol, a high potency conventional antipsychotic, is most often used in the Emergency Department. Haloperidol causes less hypotension, fewer anticholinergic side effects, and less decrease in seizure than lower potency “conventional” antipsychotic agents such as chlorpromazine (6). Patients receiving haloperidol, however, can experience acute dystonias (13). A sigmoidal dose-effect curve has been described between 2.5 mg to 15 mg for intramuscular haloperidol given within the first 4 h of treatment. Doses exceeding 15 mg are not associated with any additional benefit and actually yield lesser degrees of improvement. Higher doses also lead to an increased risk of adverse effects (14).
Over time, however, many emergency physicians have adopted a dosing technique called “rapid tranquilization” that utilizes an initial dose of 5 mg of intramuscular haloperidol, patient reassessment in 30 min for resolution of agitation, and an additional 5 mg dose at that time if needed. This technique frequently overestimates the dosing requirements necessary for the control of agitated behavior. An alternative technique begins with a 2-mg intramuscular dose. The dose is doubled for the second injection in 30–45 min if necessary (15). The cumulative dose needed to resolve the target symptoms suggests the oral dose that may be needed when the patient is treated with oral medication.

Numerous studies have implicated parenteral use of antipsychotics and QTc prolongation. The degree of QTc prolongation caused by specific antipsychotics is constantly in debate. A recent article showed an increase in “QTc prolongation ranging from 4–6 ms for haloperidol” (16). The study notes that the amount of prolongation is dependent on the individual and therefore it may be more appropriate to measure the patient’s mean change from baseline QTc. Although it has yet to be determined what degree of increase is clinically dangerous, most feel that patients with a QTc < 440 ms are at low risk of dysrhythmia.

Droperidol is a butyrophenone neuroleptic closely related to haloperidol. Intramuscular droperidol had the reputation of being a more rapid and reliable agent for the control of acute agitation compared with haloperidol (17). It has a rapid onset of action and produces greater sedation than haloperidol. The shorter serum half-life of droperidol, 2.2 h, after intramuscular injection is thought to be an advantage in many patients over haloperidol, which has a half life of 10 to 19 h (18). Patients treated with droperidol have significantly lower sedation scores than those treated with lorazepam within the first hour (19). Originally thought to have few undesirable side effects compared with haloperidol and lorazepam, droperidol was once considered a popular choice for control of agitation and sedation in the ED. Droperidol has been associated with dose-dependent prolongation of the QTc, however, which has led to a black box warning in the United States and withdrawal from use in the United Kingdom (20–22). Recent literature has critically questioned the validity of the black box warning. A review article by Kao et al. contends, “The recent black box warning appears to have originated from post-marketing surveillance data rather than data reported in the peer-reviewed medical literature. . . although droperidol has been associated with prolonged QT intervals, clinically significant adverse cardiovascular events appear to be rare” (23). The review maintains, “The evidence is not convincing for a causal relationship between therapeutic droperidol administration and life-threatening cardiac events” (23). A more definitive study is probably warranted before a final judgment regarding droperidol’s safety can be established.

COMBINATION THERAPY: CONVENTIONAL ANTIPSYCHOTICS AND BENZODIAZEPINES

A commonly used regimen for treatment of acute agitation is 5 mg of intramuscular haloperidol and 2 mg of intramuscular lorazepam given simultaneously. This combination can be mixed together in the same syringe if used immediately (1). The combination approach was initially proposed to minimize the likelihood of producing extrapyramidal effects and minimizing the need for additional doses of haloperidol. The combination approach does control the patient but increases the risk of side effects of two agents compared with one. The added sedation caused by this combination may delay additional assessment by interview and mental status evaluation.

NEWER ATYPICAL ANTIPSYCHOTIC AGENTS

Atypical antipsychotics have replaced conventional antipsychotics in the long-term treatment of chronic disorders such as schizophrenia. They are also playing an increasingly important role in the control of symptoms of the acutely psychotic patient. Their unique pharmacology has a broader spectrum of response with a lower side-effect burden. This improved side-effect profile is better accepted by patients acutely leading to enhanced levels of satisfaction and compliance with regard to long-term treatment. Therefore, the preliminary studies show that there is a greater probability that the patient will continue to take such agents if long-term therapy is needed (24). Olsson et al. found that patients treated with newer atypical antipsychotics tended to be less likely to become medically noncompliant than those treated with conventional antipsychotic agents (25).

Currently, ziprasidone (Geodon®) and olanzapine (Zyprexa®) are available in intramuscular forms, making them reasonable choices for treatment of acute agitation in the ED. Both olanzapine (Zyprexa® Zydis®) and risperidone (Risperdal® M-TAB™) are available in dissolvable oral tablets. The time to peak concentration between these two formulations is significantly shorter for risperidone compared with olanzapine and should be the preferred treatment when rapid control of agitation is required and an oral form is to be given. Dissolvable forms do not have a faster onset of action compared with any other orally dosed medication.
In terms of affinity for neuroreceptors, ziprasidone has the highest serotonin-2A/dopamine-2 ratio, which gives it a unique characteristic compared with conventional typical agents, which probably contributes to the lower incidence of extrapyramidal symptoms and enhanced therapeutic efficacy (26–28). Ziprasidone has a high affinity for several other serotonin receptor subtypes including 5-HT2C, 5-HT1A, and 5-HT1D, which may also contribute to its effects (29).

Blockage of the postsynaptic dopamine receptors in the nigrostriatal pathway produces movement disorders, such as dystonia. The potent 5HT2A antagonistic effects, as well as other receptor effects, decrease the potential for extrapyramidal symptoms, including dystonia and akathisia, which can appear acutely more commonly with conventional antipsychotics.

The benefits of intramuscular ziprasidone in significantly reducing acute agitation associated with psychosis have been shown in a double-blind, randomized trial (30). The results of the trial showed that ziprasidone in the 20-mg dose did not cause extrapyramidal symptoms, akathisia, respiratory depression, tachycardia, or excessive sedation. Moderate somnolence was the most frequent adverse event reported. The effect was noted within 15 min after the first dose and lasted 4 h. There was no evidence of any clinically relevant change in the electrocardiogram (ECG). The manufacturers of ziprasidone (Pfizer) report a clinical trial on patient volunteers: ECGs were obtained at the time of maximum plasma concentration after two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg). The QTc for the ziprasidone group produced a 4.6-ms prolongation after a 20-mg dose and a 12.8-ms prolongation with the 30-mg dose. This QTc increase was less than that seen in the haloperidol group: a 7.5-mg dose of haloperidol produced a QTc prolongation of 6.0 ms; a 10-mg dose produced 14.7-ms prolongation. No patient in this study had a QTc interval exceeding 500 ms (31).

Ziprasidone has not been associated with torsade de pointes, sudden death, or increased cardiac mortality, and only rarely produces QTc intervals above 500 ms (32,33). It is important to be aware of the associated effects on the QTc and caution should be used in implementing treatment to those patients with cardiac disease with this and other antipsychotic agents until safety in this patient population has been better established. Some recommendations include withholding antipsychotic medication if the QTc is above 500 ms or discontinuing the medication if the QTc increases by >25% after administration. In a case study of overdose with ziprasidone, 2400 mg produced a QTc of 445 ms (34). Similar findings were reported in other cases. Thus far, no fatalities have been associated with ziprasidone overdose (35). A review on the subject of fatalities with these atypical antipsychotics has failed to show a greater risk with ziprasidone compared with other agents (35). The effects of all antipsychotics on QTc prolongation is multifactorial. Propensity for a change in the QTc with the use of antipsychotics is increased when they are used in conjunction with other medications that cause QTc prolongation or if a patient has pre-existing metabolic disturbances (16). A possible genetic link for predisposition may also play a role in development and extent of QTc prolongation. Table 1 lists factors associated with increased risk of QTc prolongation and development of torsades de pointes (16,36). A clinician may choose to withhold antipsychotics if the patient is known to have any of these pre-existing factors. Obviously, in the ED, not all of this information is always readily available.

In comparison with intramuscular haloperidol in a population of admitted psychiatric patients, intramuscular ziprasidone has been found to be significantly more effective in reducing symptoms of acute agitation (37). Intramuscular ziprasidone does cause some adverse effects such as headache, dizziness, nausea, somnolence, and pain at the injection site (30). Dose-related somnolence has been the most frequently reported treatment-emergent adverse event.

Ziprasidone seems to cause less weight gain with long-term use than other atypical antipsychotics. Many studies term ziprasidone’s effects to be “weight neutral,” although some patients may experience weight gain (38). To date there are no identified patient characteristics that would suggest a patient will have weight gain with chronic therapy (38). Ziprasidone has been associated with few reports of new-onset diabetes. It is the FDA’s position that the side effect of new-onset diabetes is a class effect for all of the atypical antipsychotics, although some of the medications may be associated with

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<th>Table 1. Factors Associated with Increased Risk of QT Prolongation and Torsades de Pointes</th>
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<td>Pre-existing prolonged QTc</td>
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<td>Hypokalemia/hypomagnesemia</td>
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<td>Genetic polymorphisms of gene coding cardiac ion channels</td>
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<td>or enzymes in liver metabolizing drugs</td>
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<td>Congestive heart failure</td>
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<td>Cardiac dyshrhythmias</td>
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<td>Combination of drugs (ion channel blockers, cytochrome P450 enzyme inhibitors)</td>
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Intramuscular Benzodiazepines and Antipsychotics
higher rates of causation (39). The considerations of weight gain and glucose regulation are issues that have little effect on the use of the medication in the acute setting, as in the ED, but large effects on choices for continuation therapy.

The standard initial dose of ziprasidone is 10 or 20 mg (consider the lower dose in elderly patients), and begins to have an effect in 15–20 min. The time to prepare the injection may increase this time with an additional 2 min required to place the drug into solution (40). The recommended interval from the first to second injection of ziprasidone is 4 h. A second injection of ziprasidone has been only infrequently needed in clinical evaluations.

Another atypical antipsychotic agent, olanzapine (Zyprexa®), has recently been approved for intramuscular use. Olanzapine has a combined serotonin and dopamine antagonist action with a greater affinity for serotonin receptors (41). The antihistaminergic potency of olanzapine is over 160 times that of diphenhydramine (42). This may explain the associated adverse effect of sedation and weight gain. As with other atypical antipsychotics, olanzapine has been associated with an increased risk of new-onset diabetes or serum glucose dyscontrol (39). A recent review published by the FDA documented 237 reports of olanzapine-induced diabetes or hyperglycemia, most of which appeared within 6 months of starting the therapy (43). These reports, along with that of weight gain over time, may be a consideration for the treatment of the acute agitated patient in the ED if eventual transition to the same oral medication is anticipated (44).

Intramuscular olanzapine has been found to be more effective than either haloperidol or placebo for managing acute agitation in schizophrenic patients at the earliest time point measured in a double-blind study (45). Olanzapine has been well tolerated in studies. No patients treated with olanzapine experienced the acute dystonia that occurred in 7% of the haloperidol treated patients (46). Olanzapine was found to have similar efficacy to lorazepam in treatment of dementia and bipolar mania (47,48). One potential drawback with the use of intramuscular olanzapine for acute agitation in the ED is the possibility of the medication causing postural hypotension. In a recent study, olanzapine showed an approximate 12% increase in postural hypotension compared with an approximate 3% increase with haloperidol (49). A study by Breier et al. has shown olanzapine to be effective in reducing agitation by a dose-dependent relationship. The study concluded that 10 mg of i.m. olanzapine was more effective then 2.5 mg. When smaller doses were given initially, the need for re-dosing was frequent (50). The use of olanzapine in conjunction with benzodiazepines has been shown to cause a hypoventilatory syndrome and therefore is not recommended (51).

Due to olanzapine’s fairly recent FDA approval for the treatment of acute agitation by means of intramuscular administration, additional studies of olanzapine used in more severely ill patients and patients with concomitant medical illnesses are needed to determine the most effective dosing regimen, need for use of adjunctive medications, and to obtain a comprehensive safety profile (52).

**CONCLUSION**

Agitation is a common and often frustrating complaint in the Emergency Department. There have been great improvements in the pharmacological treatment of the acutely agitated or psychotic patient in the past few years. Historically, older neuroleptics such as chlorpromazine and barbiturates were commonly used. Droperidol was a popular choice until the FDA black box warning. The classical treatment of patients with haloperidol or haloperidol plus lorazepam has been used effectively for many years. The adverse effects range from excessive sedation to extrapyramidal symptoms to potential development of neuroleptic malignant syndrome. The risks and benefits of these medications are well known due to their vast use over a long period of time.

Newer, atypical antipsychotics are recognized as a breakthrough for the treatment of psychosis and acute agitation. Intramuscular ziprasidone is used in such situations due to its rapid onset and low incidence of side effects. The QTc prolongation has been excessively studied and has not been linked to any life-threatening conditions. Intramuscular olanzapine is also a reasonable choice for therapy. Olanzapine has been shown to be effective in controlling agitation in the clinical setting. As more prospective studies are performed comparing olanzapine with other atypical and conventional treatments, a more comprehensive efficacy and safety profile can be established.

Atypical antipsychotics are generally well tolerated by patients. The decreased amount of sedation caused by atypical medications compared with conventional medications allows the patient’s agitation to be controlled and yet still allows the patient to be able to participate in his or her care. This leads to shorter ED stays and increased patient satisfaction. Unfortunately, a subject not always considered is management of the patient after leaving the ED, both over the next few days and in the long-term setting. Long-term compliance with atypical antipsychotics is dramatically improved over conventional treatments secondary to their improved side-effect profile. Finding a medication that is efficacious and well tolerated for use in both the acute and long-term settings would be ideal.
Atypical antipsychotic medications offer new hope that this type of medication is possible. A more comprehensive risk/benefit analysis will be possible as more research is performed and clinicians learn which medications are the best in particular settings.

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