A Comparison Study of the Efficacy of Rapid Titration Quetiapine and Haloperidol in Agitated Adults in an Emergency Setting*

Akikur Mohammad¹, Eugene Laska², Marius Campaneau¹, Fauzia Syed¹, Rebecca Ninah¹, Joseph Wanderling², George Simpson¹#

¹Department of Psychiatry, LAC-USC, Los Angeles, CA, USA
²Nathan Kline Institute, New York, NY, USA
Email: #gsimpson@usc.edu

Received 19 March 2014; revised 18 April 2014; accepted 15 May 2014

Abstract

Objective: Intramuscular (IM) Benzodiazepines and/or Haloperidol alone or with benzodiazepines are frequently used to treat agitation. Based on emerging literature regarding Quetiapine used for the control of anxiety we examined Quetiapine as a possible alternative in selected cases.

Methods: This study was a single-blind randomized study comparing Quetiapine PO (300 mg) with a combination of Haloperidol (5 mg), Benztropine mesylate (2 mg) and lorazepam (2 mg) administered IM to treat agitated patients seeking care in a busy psychiatric emergency setting. Male or female patients (18 - 60), deemed by the attending (admitting) psychiatrist to be indicative of agitated and/or aggressive behavior and had a Positive and Negative Syndrome Score-Excited Component (PANSS-EC), as evaluated by the Research Psychiatrist, and total score equal to or greater than 15. Patients deemed competent were randomized into one of the following treatment groups: Quetiapine 300 or Haloperidol 5 mg, benztropine mesylate, or lorazepam given by the IM route. Two scales, PANSS-EC and CGI-C were used to assess patients in the trial. The primary outcome measure PANSS-EC at 2 hours after administration of the medication. Results: Sixty-eight patients were included in the study. There were no significant treatment group differences in baseline condition. There was no significant difference between the two conditions. There was, however, a significant within-group decrease from baseline condition. Conclusion: Finding no significant differences suggests that in general the two treatments were equivalent. To sum up, Quetiapine 300 mg as a single dose appeared safe and effective in agitated patients treated in an ER. The results were similar to a comparison group receiving an intra-muscular combination of Haloperidol, Lo-

*Previously presented as a poster at The American College of Neuropsychopharmacology 2009.
This was an investigator initiated study which received grant support from Astra Zeneca,USA. The design implementation data analysis and write up involved only the authors.
#Corresponding author.

razepam and Benztropine. This study has significant limitations. The study was single blind and the use of a placebo would have strengthened the design but would be considered unethical. The sample size was relatively small and the group of patients who come to the ER may not be representative of the population of patients who visit across the country. And finally it was a select subgroup who made up the study population and who were probably less severely ill than other subjects who came to our ER.

Keywords
Quetiapine (Oral), Haloperidol (Parenteral), Agitation, Excitement, Psychoses

1. Introduction
The treatment of agitation in the psychiatric emergency room (ER) has changed little in the last decades. While intramuscular (IM) benzodiazepines are often used, haloperidol (frequently combined with a benzodiazepine and/or an anticholinergic) is still the treatment of choice in many places. Studies of liquid preparations represent a possible alternative for some patients, given their faster absorption compared with tablets or capsules similar to rapid dissolve tablets. Even liquids are not always convenient in a busy ER. The ideal would be a range of options, for example, benzodiazepine or antipsychotic and in turn tablet/capsule, liquid, rapid dissolve tablets or IM preparations. A recent study showed that inhaled loxapine may offer a further option to control agitation, particularly, as peak concentrations are obtained comparable to parenteral administration [1]. The availability of the second-generation antipsychotics (IM preparations) has not altered the situation significantly perhaps because of the increased cost of these preparations. Recently one of us (RM) began to use quetiapine in increasing dosages up to 300 mg in selected patients seeking treatment at the USC ER, based on emerging literature regarding quetiapine use for the control of anxiety [2]-[4].

Based on our initial personal experience, we felt that further study was warranted to examine the potential use of this preparation as a possible alternative in selected cases compared with the IM preparation.

2. Methods
This study was a single-blind randomized study comparing Quetiapine PO (300 mg) with a combination of haloperidol (5 mg), benztropine mesylate (2 mg) and lorazepam (2 mg) administered IM to treat agitated patients seeking care in a busy psychiatric emergency setting. Male or female patients, aged 18 - 60 years, who presented at the ER with a diagnosis of agitation or aggressive behavior whose symptoms could include restless pacing, inability to sleep, physical aggression towards others as well as other symptoms deemed by the treating (admitting) psychiatrist to be indicative of agitated and/or aggressive behavior were referred to the research team. Patients with a presumed diagnosis of schizophrenia, bipolar disorder, substance abuse and psychosis or other mood disorders with psychosis and had a Positive and Negative Syndrome Score-Excited Component (PANSS-EC) (excitement, hostility, tension, uncooperative, poor impulse control) total score of equal to or greater than 15, a Clinical global Impression of Change (CGI-C) of 5 or less and to meet DSM-IV criteria for the diagnosis of psychosis NOS (not otherwise specified) were selected for the study. No attempt was made to control for previous episodes or drug use.

Patients diagnosed with the disorders under study are generally considered to be a vulnerable population. To protect this vulnerable population, the capacity of the patient to consent was determined by a clinician who was independent of the research team. Patients deemed competent and in need of medication were referred to the research team who described the study including the different routes of administration and potential side effects of each medication. Patients excluded from the study received routine treatment. Patients were excluded if they were unable to understand the study, unable to give consent, were receiving anticoagulant therapy, had serious medical illness, were female who were pregnant or nursing, or who had an acute withdrawal from any illicit drugs. Eligible patients were randomized into one of the following treatment groups: Quetiapine 300 mg PO or haloperidol 5 mg, benztropine mesylate 2 mg, lorazepam 2 mg given by the IM route. Randomization was carried out in advance, blocks of four by a coin toss. Sealed envelopes marked on the outside and with Quetiapine
or Haloperidol on a folded paper and were prepared in advance and stored in blocks of foam in the nurse’s sta-
tion.

As in a previous study conducted at this site [5], two scales, PANSS-EC and CGI-C were used to assess pa-
tients in the trial. The primary outcome measure was PANSS-EC at 2 hours after administration of the medica-
tion. The secondary outcome measure was a binary indicator of improvement defined as a CGI-C score of
“much improved” or “very much improved” at 2 hours and/or a 20% reduction in PANSS-EC 2 hours following
administration of the medication.

The PANSS-EC was measured at baseline, and at 1, 2, 4 and 8 hours after medication. The CGI-C Severity
was measured at baseline and the CGI-C Improvement was measured at 1, 2, 4 and 8 hours after medication.
Extrapyramidal symptoms (EPS) were also evaluated at these times. Both lying and sitting blood pressure and
pulse were measured at 15 and 45 minutes and at 1, 2, 3, 4, 6 and 8 hours and adverse events were documented
throughout the 8-hour study.

Statistical Analysis

The data are described together with the results of the analysis. Tests of differences in proportions utilized a chi-
squared statistic. We used an analysis of covariance (ANCOVA) with baseline as the covariate to analyze the
primary outcome measure, PANSS-EC at hour 2 for those awake. Note that, formally, this is not an intent-to-
treat (ITT) analysis since not all patients who were randomized are included in the analysis set. However, argu-
ably, this analysis together with the probability of being awake does include all (but a few) randomized subjects
and so might be nearly equivalent to an ITT analysis. The mean time course of the four post treatment PANSS-
EC evaluations was analyzed using a mixed model repeated measures (MMRM) approach under the assumption
that the missing data are “missing at random”. This analysis is based on the ITT principle. The MMRM model
included terms for age, adjusted baseline, hour, treatment and the two interactions: adjusted baseline by hour and
hour by treatment. A mixed model was used to analyze CGI-C binary indicators of improvement. The covariates
were the same as those used in the PANSS-EC.

3. Results

Sixty-eight patients were included in the study. An additional four patients were randomized to haloperidol but
were excluded from the analysis because they had neither baseline nor post-treatment data. There were no si-
nificant treatment group differences in baseline PANSS-EC, baseline CGI-C, mean age and in the proportion of
males. Further characteristics of the sample are shown in Table 1.

At the 2-hour timepoint, 10 of the 30 haloperidol patients and 9 of the 38 quetiapine patients were asleep at
the time the PANNS-EC was administered. These proportions were not significantly different based on a chi-
squared test (See Table 5). The least square means from the ANCOVA were −11.3 for haloperidol and −11.7
for quetiapine and the contrast was not significant. There was, however, a significant within-group decrease
from baseline for both treatments.

A chi-squared test of the secondary outcome variable—20% or more decrease in PANSS-EC at hour 2—also
did not yield a significant treatment difference (see Table 2). Nineteen of the 20 haloperidol patients who were
awake and all of the quetiapine patients who were awake had a reduction of at least 20% in PANSS-EC score.

There were 5 cases among the 68 patients for which the PANSS-EC were missing at all 4-times and these pa-
tients were excluded in the MMRM analysis of differences in the time course. Treatment and hour by treatment
effects were not significant and there were no significant treatment differences at any hour (see Table 3 for least
square means and standard errors from this analysis).

A chi-squared test of improvement based on the CGI-C at hour two yielded a marginally significant treatment
effect. All haloperidol patients and 79% of the quetiapine patients were “much” or “very much” improved (p =
0.0766). A logistic regression on the same measure, using baseline CGI-C severity as a covariate, failed to con-
verge (likely due to improvement of all haloperidol cases (see Table 4). A second analysis based on the more
demanding condition for success of “very much improvement” did converge and the treatment difference was
not significant.

There were 4 cases among the 68 patients for which the CGI-C were missing at all 4 time points and these pa-
tients were excluded from the mixed model analysis. As in the logistic analyses at hour 2, the model for “much”
or “very much” improved failed to converge at hour 2. For the model in which a responder was defined as very
Table 1. Demographic characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>IM haloperidol Clocktail N = 34</th>
<th>Oral Quetiapine N = 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>35.8</td>
<td>36.1</td>
</tr>
<tr>
<td>Number Men/Women</td>
<td>28/6</td>
<td>29/9</td>
</tr>
<tr>
<td>Number by Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>White</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Number with at least 20% reduction in PANNS-EC for those awake.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>20% reduction</th>
<th>Hour 1</th>
<th>Hour 2</th>
<th>Hour 4</th>
<th>Hour 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haldol Cocktail</td>
<td>Yes</td>
<td>24</td>
<td>19</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>No</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Least square means (SE) for change in PANSS-EC for those awake.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hour 1</th>
<th>Hour 2</th>
<th>Hour 4</th>
<th>Hour 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haldol Cocktail</td>
<td>−7.7</td>
<td>−11.0</td>
<td>−12.8</td>
<td>−16.1</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>(0.76)</td>
<td>(0.82)</td>
<td>(0.82)</td>
<td>(0.74)</td>
</tr>
<tr>
<td>(0.65)</td>
<td></td>
<td>(0.69)</td>
<td>(0.70)</td>
<td>(0.63)</td>
</tr>
</tbody>
</table>

Table 4. Number with CGI improvement for those awake.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CGI Improvement</th>
<th>Hour 1</th>
<th>Hour 2</th>
<th>Hour 4</th>
<th>Hour 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haldol Cocktail</td>
<td>Very much</td>
<td>12</td>
<td>14</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>much</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>minimal or worse</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Very much</td>
<td>7</td>
<td>19</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>much</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>minimal or worse</td>
<td>17</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

much improved, the treatment and hour by treatment interaction were not significant and there were no significant treatment differences at any hour. However, there was a marginally significant treatment difference at the first hour. The estimated responder rates were 0.357 for haloperidol and 0.132 for quetiapine (p = 0.0778) (Figure 1 shows this as percentage of patients who showed improvement). No patient required a second dose of medication during the eight-hour study period.

Adverse Events

The adverse event profiles of the two treatments were also similar. Sedation was the most prominent side effect reported for both treatments. As seen in Table 5, some patients were already asleep at the one-hour timepoint, the maximal number occurred at four hours and the effect was still present to a significant degree at 8 hours. During the study, there were 11 patients with low diastolic blood pressures (40 - 60 mmHg) in the haloperidol group and 12 patients with low diastolic blood pressures in the quetiapine group. This included 4 patients with low blood pressures at baseline.

No cases of syncope or hypotensive collapse were noted. Extra-pyramidal side effects were absent in both groups.
4. Discussion

Although the finding of no significant differences does not prove that there are no differences, the present study suggests that in general the two treatments were similarly effective in the treatment of acute symptoms of agitation in the emergency setting. The haloperidol mixture did have an almost statistically significant advantage on one of the secondary outcome measures: a binary indicator of improvement defined as a CGI-C score of “much improved” or “very much improved” at 2 hours and/or a 20% or greater reduction in PANNS-EC 2 hours following administration of the medication. This difference is unlikely to be attributed solely to the patient being asleep, since the treatments did not differ on that measure. However, as might be expected from the more rapid absorption of an I.M injection, changes early on favored the I.M cocktail. It must be noted that no adjustments were made to control the fairly wide error rate to account for the many statistical tests that were conducted.

The use of mixtures of medication (i.e., benzodiazepine plus haloperidol) is based on the belief that the sedative effect of lorazepam is helpful for controlling agitation (short term) [6] [7] and the antipsychotic adds to this and has a longer-term effect. The use of benzodiazepine in the haloperidol cocktail was also motivated in part to reduce the amount of haloperidol to an antipsychotic dose and thereby reduce the potential for acute dystonia, akathisia and the serious side effects mentioned below. The rational use of a combination is based on the requirement that it is superior to each of its components used alone and indeed some studies of the haloperidol cocktail do suggest that this is the case [8] [9]. Fortunately, the use of rapid neuroleptization-high doses of high potency antipsychotics is now a thing of the past. This practice was associated with significant side effects, including sudden death, neuroleptic malignant syndrome as well as EPS. It is our impression that in a very busy overcrowded ER, there still seems to be a sense of security around the use of an IM preparation.

To sum up, quetiapine 300 mg as a single dose appeared safe and effective in agitated patients treated in an ER. The results were similar to a comparison group receiving an intra-muscular combination of haloperidol, lorazepam and benztprine. There are suggestions that the IM group responded more rapidly and were more rapidly sedated. The data do reinforce the availability of a range of treatment options for treatment of agitation; liquids, tablets/capsules or even inhalations [6], which in selected patients may avoid the use of intramuscular preparations. This study has significant limitations. The study was single blind, the sample size was relatively small and the select group of patients who come to the ER may not be representative of the population of patients who visit ERs across the country. The study did not include placebo whose use in this clinical context is unethical. No adjustments were made to control the family wise error rate to account for the many statistical tests that were conducted. To demonstrate the equivalence of two treatments based on a possibly more appropriate non-inferiority analysis, requires a substantially larger number of patients than were used here. Finally, since patients who were dozing or appeared asleep were not awakened, it is possible that the number of side effects is
underestimated and it is probable that the selected subgroup of patients were less severely ill than other patients who are brought to our ER.

Acknowledgements

Dr. Abderahmane Richane
Dr. Arastou Aminzadeh
Dr. Brenda Quon
Dr. Carolina Bradshaw
Dr. Catherine Scott
Dr. Darin Signorelli
Dr. Gayane Begoyne
Dr. Grace Akra
Dr. Jairo Gomez
Dr. Joseph Mirkovich
Dr. Kamal Bijanpour
Dr. Linda Wang
Dr. Robert Barker
Dr. Simargit Gill

References


Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

Other selected journals from SCIRP are listed as below. Submit your manuscript to us via either submit@scirp.org or Online Submission Portal.