Rapid Tranquilization With Olanzapine in Acute Psychosis: A Case Series

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Acute high-dose loading strategies (rapid neuroleptization) with the first-generation antipsychotics administered orally or parenterally, alone or combined with benzodiazepines, have been a commonly used treatment paradigm for controlling acutely agitated psychotic patients. The rationale was to achieve high plasma levels of drug within a shorter time period, resulting in rapid symptom mitigation. However, studies have shown that rapid neuroleptization with first-generation antipsychotics is associated with a greater incidence of side effects. To our knowledge, loading strategies with second-generation antipsychotics have not been investigated, primarily owing to a need for dose titration. Olanzapine, a second-generation antipsychotic, is well tolerated in doses ranging from 5 to 20 mg. The objective of this report was to determine experience with the use of up to 20 mg of an oral loading dose of olanzapine administered within 4 hours in the treatment of patients early in an acute psychotic phase of their illness. In the reported case series of 57 patients, olanzapine initiated at 15 to 20 mg/day was a safe and effective medication for rapidly calming the agitation of acutely agitated psychotic patients (rapid tranquilization). Furthermore, dose reduction over 2 to 3 weeks was achieved in a number of patients without appreciable loss of efficacy.

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Rapid neuroleptization with the first-generation antipsychotics was a commonly used strategy to control agitation and psychotic symptoms in patients suffering from an acute psychotic episode. This practice usually involved the use of high doses of antipsychotics administered orally or intramuscularly, either alone or in combination with a benzodiazepine (i.m. medication once every 30–60 minutes until symptoms are controlled).[1,2] The drugs were titrated until clinical improvement was observed or overt sedation or side effects emerged.[3] The route of administration depended on the severity of the psychotic episode, with intramuscular preparations being used in the most agitated patients, who are often aggressive and hostile. Intramuscular preparations of haloperidol or fluphenazine have been used most commonly. The oral route was preferred in patients who were agitated and psychotic but willing to take oral medication. Candidate patients included those with schizophrenia, mania, psychosis characterized by agitation, aggressiveness, combativeness, and psychosis with depressive symptoms.[4]

The existing body of literature on rapid neuroleptization is ambivalent about this method. Earlier reports advocated the use of up to a maximum of 100 mg/day of haloperidol i.m., resulting in a rapid calming effect with no increase in side effects (see Donlon et al.[5]). However, a number of double-blind studies have demonstrated that rapid neuroleptization is no more effective than starting patients on a moderate dose such as 10 mg/day of haloperidol.[6] The use of rapid neuroleptization has declined because of 2 major drawbacks: higher doses are associated with more neurologic side effects, including extrapyramidal symptoms,[7,8] and a number of studies have shown that the clinical response to higher doses (both rate and amount of improvement) was no greater than that seen with more moderate doses.[5,7–10] Thus, the risks far outweigh the benefits of using this therapy with the first-generation antipsychotics.

To our knowledge, very little literature exists for rapid neuroleptization using the second-generation antipsychotics. There are 2 main reasons for this lack of research:

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many of the newer agents have to be titrated, and none of these drugs are commercially available to date in the United States in an intramuscular formulation. There is also a clinical perception that the newer agents are not very effective in the management of acute agitation. Olanzapine is a newer antipsychotic that does not require titration and is well tolerated at the recommended daily dose of 5 to 20 mg. Preliminary evidence suggests the safety and efficacy of olanzapine in an intramuscular formulation for agitation at a dose level that corresponds to the higher end of the oral dose range of olanzapine in terms of peak plasma levels of drug.[11] Higher doses of olanzapine (15–20 mg/day) have also been used safely in patients with bipolar mania and schizophrenia.[12–14] Therefore, we examined a series of patients who were acutely agitated and were treated with an oral loading dose of olanzapine in a manner loosely akin to the older approach of rapid neuroleptization.

CASE SERIES COLLECTION METHOD

Psychiatrists experienced in treating agitated patients identified patients who were agitated as a result of disease exacerbation but were otherwise healthy, were good candidates for olanzapine therapy, and were willing to accept oral medication. Patients had a DSM-IV diagnosis of schizophrenia (N = 22), schizoaffective disorder (N = 8), bipolar disorder (N = 12), or other (psychosis not otherwise specified, N = 12; psychosis-bulimia, N = 2; personality disorder, N = 1). Patients with a diagnosis of organic brain disease were excluded from subsequent analysis. Many of the patients were inpatients, while some were seen in the emergency department and subsequently hospitalized owing to the severity of their symptoms. Patients who were orally treated with olanzapine at doses that exceeded 10 mg within a 4-hour period from time of first dose were noted, and their status in terms of response and tolerance to treatment was assessed for up to 24 hours in the acute phase. Efficacy was assessed using the Clinical Global Impressions scale (CGI) at approximately 24 hours or at the discretion of the physician. Concomitant medications within the 24-hour period were also recorded. Subsequent to the acute phase, patients were followed over a subsequent 2- to 3-week period, during which time the ability to reduce the dose into the range of 10 to 15 mg/day was assessed. Safety was monitored according to usual clinical practice. The common features seen in these cases in terms of response to treatment and tolerability were then identified and compared with the experience of using a rapid neuroleptization approach with first-generation antipsychotics.

CASE DESCRIPTIONS

Dosing

Fifty-seven patients received at least 10 mg of olanzapine within the first 4 hours of being seen by the physician.

Table 1. Mean Olanzapine Dose Baseline to Endpoint for Patients Receiving ≥ 20 mg (N = 46) and < 20 mg (N = 11) in the First 4 Hours of Treatment

Olanzapine Dose	Baseline	12–24 h	72 h	1–2 wk	End
≥ 20 mg	20.43	19.13	19.43	17.16	14.74
< 20 mg	15.00	15.91	17.27	17.78	16.88
Total	19.39	18.51	19.00	17.28	15.20

Of these patients, 1 (1.8%) received 30 mg of olanzapine, 2 patients (3.5%) received 25 mg, 43 patients (75.4%) received 20 mg, and 11 patients (19.3%) received 15 mg (Table 1). The mean starting dose of olanzapine was 19.39 mg at 4 hours, 18.51 mg at 12 to 24 hours, 19.00 mg at 72 hours, 17.28 mg at 1 to 2 weeks, and 15.20 mg at the final visit (usually at 3–4 weeks). Interestingly, those patients who received 20 mg or more of olanzapine at 4 hours could be successfully managed with a lower dose at final visit, whereas those who received less than 20 mg within the first 4 hours had to have their dose escalated before being stabilized at a lower dose (see Table 1).

Efficacy Measures

The CGI was used to assess agitation on a scale of 1 to 7 as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Patients had a mean score of 2.43 at 12 to 24 hours and improved steadily until the last visit, at which time the average score was 1.81. Four patients (7%) showed a clinical worsening, and 1 patient was unchanged (Tables 2 and 3).

Level of care was scored on a scale of 1 to 3 as follows: (1) in hospital, needs major supervision; (2) in hospital, needs only minor supervision; and (3) out of hospital. All patients started out as inpatients. Five patients were discharged by the end of the variable observation period, with the majority of the patients remaining in the hospital but under minimal supervision (see Table 2).

Tranquilization was scored on a scale of 1 to 5 as follows: (1) fully alert and active; (2) alertness and activity reduced, eyes open and following movement, etc.; (3) alertness and activity greatly reduced; eyes closed, but open if, for example, name called; (4) sleeping, rousable, not confused, awakes spontaneously to urinate, etc., does not return to sleep immediately following rousing; and (5) deeply asleep, not rousable if name called, rousable with difficulty on physical stimulation, confused ("drunk") if roused, returns to sleep immediately after rousing unless strongly stimulated. The physicians used their clinical judgment in defining this scale to categorize patients according to level of alertness. Patients generally remained alert and active during olanzapine therapy (see Table 2). Concomitant medications were recorded but showed no obvious patterns related to the success or failure of using olanzapine in this manner.

Adverse events were minimal. Extrapyramidal symptoms were few; these resolved spontaneously or, in 1 case,

Table 2. Efficacy Measures Baseline to Endpoint for Patients Receiving Olanzapine, ≥ 20 mg (N = 46), and Olanzapine, < 20 mg (N = 11), in the First 4 Hours of Treatment[a]

Efficacy Measure	Baseline	12–24 h	72 h	1–2 wk	End
Mean CGI score					
Both groups		2.43	2.21	1.80	1.81
≥ 20 mg		2.41	2.28	1.85	1.91
< 20 mg		2.45	2.09	1.78	1.71
Mean level of care score					
Both groups	1.14	1.38	1.68	2.02	2.07
≥ 20 mg	1.19	1.44	1.77	2.03	2.04
< 20 mg	1.00	1.30	1.40	2.00	2.20
Mean tranquilization score					
Both groups	Patients were generally alert	1.51	1.37	1.05	1.00
≥ 20 mg		1.40	1.38	1.03	1.00
< 20 mg		2.00	1.40	1.13	1.00

[a]Abbreviation: CGI = Clinical Global Impressions scale. CGI used to measure improvement from baseline.

Table 3. Patients Experiencing Clinical Worsening or No Change While Taking Olanzapine[a]

Patient No.	Baseline	12–24 h	72 h	1–2 wk	End
3					
Daily dose, mg	20	20	15	15	15
CGI score		1	1	4	3
5					
Daily dose, mg	20	20	20	20	20
CGI score		2	4	5	
18					
Daily dose, mg	20	30	30	30	0
CGI score		4	4	3	4
52					
Daily dose, mg	15	15	15	15	15
CGI score		3	3	3	3
53					
Daily dose, mg	30	10	10	10	10
CGI score		3	7	1	6

[a]Abbreviation: CGI = Clinical Global Impressions scale. CGI used to measure improvement from baseline.

Table 4. Safety Profile Baseline to Endpoint for Olanzapine in Patients Receiving ≥ 20 mg and < 20 mg in the First 4 Hours of Treatment

	12–24 h		72 h		1–2 wk		End	
Adverse Event	≥ 20 mg (N = 42)	< 20 mg (N = 9)	≥ 20 mg (N = 40)	< 20 mg (N = 10)	≥ 20 mg (N = 33)	< 20 mg (N = 8)	≥ 20 mg (N = 26)	< 20 mg (N = 7)
Dystonia, N (%)	0	0	0	0	0	1 (13%)	0	1 (14%)
Akathisia, N (%)	1 (2%)	0	1 (3%)	0	0	0	0	0
Extrapyramidal, symptoms N (%)	2 (5%)	0	2 (5%)	1 (10%)	0	1 (13%)	0	0
Oversedation, N (%)	6 (14%)	3 (33%)	4 (10%)	0	1 (3%)	0	0	0
Hypotension, N (%)	1 (2%)	0	1 (3%)	0	0	0	0	0
Nausea, N	0	0	0	0	0	0	0	0

with dose reduction. Dystonia was seen in 1 patient at 2 weeks of therapy, and it was present at the patient's final visit. Other adverse events included oversedation, hypotension, and akathisia (Table 4).

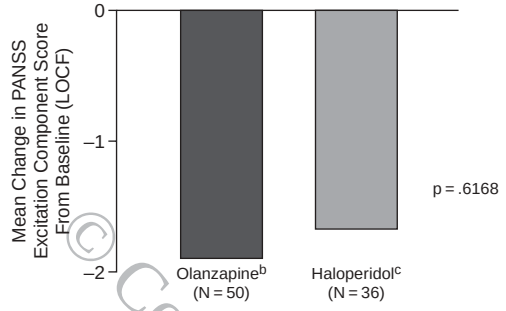
DISCUSSION

In this series of cases in a naturalistic setting, olanzapine was effective in treating acutely agitated patients when administered orally in doses higher than those used for maintenance therapy.[15] It should be emphasized that this was not a clinical study, but rather a series of cases in which experienced clinicians treated agitation as indicated with olanzapine within the recommended dose range of 5 to 20 mg. Despite the limitations of a case series, the observation that an atypical antipsychotic may be safe and effective in agitated patients when administered within an acute, high-dose loading paradigm is novel.

This oral loading dosing strategy with olanzapine differs from the rapid neuroleptization strategy used with the first-generation antipsychotics in that, with the first-generation antipsychotics, drugs were administered until a clinical response, overt sedation, or side effects (neuroleptization) were observed.[3] In this series, olanzapine was administered within the recommended daily dose range of 5 to 20 mg (except for 2 patients who received 25 mg), and the dose was not escalated beyond that range. Thus, the term *rapid tranquilization* rather than *rapid neuroleptization* more accurately describes this treatment paradigm.

There is a clinical perception that second-generation antipsychotics are not very effective in treating the acutely agitated psychotic patient. This perception is not consistent with the available evidence that second-generation antipsychotics are at least as effective as first-generation antipsychotics in controlling positive symptoms in acute patients. The perception of less efficacy in the acute phase, however, may be due to lack of intramuscular formulations and an inability to dose aggressively. Olanzapine may be an exception in terms of the latter issue, but physicians generally start patients on 10 mg/day of olanzapine, which has been demonstrated to achieve good control of psychotic symptoms.[13,14,16] The recommended starting dose of 5 to 10 mg (range, 5–20 mg/day) for olanzapine was determined on the basis of early clinical trials in which patients were capable of giving consent and thus were possibly not as acutely agitated as many of the patients who are treated in emergency departments. Two of these early studies[13,14] compared 3 fixed doses of olanzapine (5.0 ± 2.5 mg/day, 10.0 ± 2.5 mg/day, and 15.0 ± 2.5 mg/day) with placebo or 1 mg/day of olanzapine and halo-

Figure 1. Efficacy of Olanzapine Versus Haloperidol for Acute Agitation in Schizophrenia After 3 Days of Oral Administration[a]



[a]Data on file, Eli Lilly and Company, Indianapolis, Ind., 1999.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale. Agitation defined as baseline score ≥ 14 and at least 1 item ≥ 4 on the PANSS excitation component (poor impulse control, tension, hostility, uncooperativeness, and excitement).
[b]Mean ± SD olanzapine dose = 15 ± 2.5 mg/day.
[c]Mean ± SD haloperidol dose = 15 ± 5 mg/day.

peridol (15.0 ± 5.0 mg/day). Efficacy analysis, defined as mean change from baseline to endpoint in Brief Psychiatric Rating Scale scores, showed patients in the middle- and high-dose olanzapine groups to have statistically significantly greater response than placebo-treated patients in the acute phase ($p < .001$). However, the first measurement was taken between days 3 and 4; thus, data on efficacy at shorter timepoints are not available. Interestingly, a subanalysis conducted at 3 days on the efficacy of higher doses of olanzapine (15 ± 2.5 mg/day) and haloperidol (15 ± 5 mg/day) in reducing agitation shows that both olanzapine and haloperidol could reduce agitation as measured by the Positive and Negative Syndrome Scale excitation component (reference 14 and data on file, Eli Lilly and Company, Indianapolis, Ind., 1999; Figure 1).

In our case series, patients were acutely agitated and were treated as clinically indicated, not dosed according to a protocol-dosing regime. In general, the strategy of using an oral loading dose of olanzapine in this case series resulted in good control of agitation at doses higher than 10 mg. This is consistent with the established safety of olanzapine at doses up to 20 mg/day with the lack of a titration requirement. In contrast, the other second-generation antipsychotics require titrating patients upward from low doses. Hoyberg et al.[17] studied patients with acute exacerbations of chronic schizophrenia treated with risperidone and found a trend toward increased parkinsonism scores in patients treated with 5 to 15 mg of risperidone compared with patients treated with perphenazine. Similarly, Rosebush and Mazurek[18] studied the effects of low-dose risperidone (mean dose = 3.2 mg/day) versus haloperidol (mean dose = 3.7 mg/day) in neuroleptic-naive patients with acute psychotic exacerbations and found the incidence of parkinsonism to be comparable in the 2 treatment arms.

One of the problems associated with the rapid neuroleptization methods used earlier was the downward titration of dose to a maintenance level once symptom control was achieved. High doses during acute therapy made low-dose maintenance more difficult to achieve.[19] In this case series, the initial high dose of olanzapine was successfully reduced, and this approach was very well tolerated in the majority of patients. An interesting observation was made when patients were split according to starting dose. Patients who were started on 20 mg/day or higher in the first 4 hours after being seen by the physician were, in general, successfully reduced to lower doses, whereas patients started on doses lower than 20 mg/day had to have their doses escalated to achieve optimal control of agitation. This difference could be due to a number of reasons. Acute high dosing could have led to therapeutic plasma levels of drug being reached early and maintained at therapeutic levels with lower doses later. It has been generally established that early treatment of psychosis leads to better response to antipsychotic medications as well as better long-term outcomes.[20] Although speculative, it is interesting to consider whether this better response and long-term outcome could be true for agitation; rapid control of agitation could lead to a better outcome, therefore requiring less medication later on. Another explanation would be simply that rapid symptom control with the higher starting dose could have led the physicians to feel comfortable about decreasing the dose sooner. The sedation observed during treatment with olanzapine could be a benefit to some patients with acute agitation and also could have led to a lowering of the dose in a calmed patient.

Finally, it would be erroneous to assume that these patients had arrived at their final maintenance dose by the final visit. It is important to keep in mind the severity of agitation in the patients included in this case series; physicians could have been reluctant to reduce the dose to prevent any breakthrough of patients' symptoms. Also, it has been recognized that antipsychotics may take 4 to 6 weeks to achieve therapeutic efficacy,[21,22] and the final visit for most patients in this case series was after only 3 to 4 weeks. Further studies are clearly needed to evaluate whether a further reduction in dose would have been possible.

With respect to safety and tolerability, the incidence of extrapyramidal symptoms was minimal. Laryngeal and pharyngeal dystonias leading to respiratory distress, although rare, are among the side effects reported to occur more commonly with rapid neuroleptization using first-generation antipsychotics.[23] Only 1 patient developed dystonia at 2 weeks of therapy; this dystonia persisted until the last reported visit. One patient of the 57 included in this analysis had akathisia, which resolved at 72 hours when the dose was reduced to 15 mg. Sedation was seen in 17% of the patients at 12 to 24 hours, but this resolved over time. Patients generally remained alert throughout the treatment period.

Although such a series of cases cannot alone justify the use of an oral loading strategy with an atypical antipsychotic such as olanzapine without further data from randomized, controlled trials, this series supports further study of this approach. This is especially true given that the experience with first-generation antipsychotics has not been optimal using rapid neuroleptization, yet this technique is still used in clinical practice, suggesting an unmet clinical need.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), risperidone (Risperdal).

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