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Observational data on the antiagitation effect of risperidone tablets in emergency settings: A preliminary report

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OBJECTIVE: ***To provide preliminary data on the effectiveness of risperidone in tablet form in the emergency treatment of agitation.***

METHOD: ***Eighteen acutely agitated psychiatric patients who were given either haloperidol (2–5 mg intramuscular (i.m.)) or risperidone (1–2-mg tablet) were evaluated hourly using the four different agitation rating scales for 2 h. Concomitant use of lorazepam was allowed at the clinical discretion of the acute psychiatry service (APS) physician for both study groups.***

RESULTS: ***Baseline agitation scores of both groups were comparable. Both haloperidol and risperidone were found to be effective in decreasing agitation/aggression.***

CONCLUSIONS: ***This pilot study provides preliminary data suggesting that atypical antipsychotics in oral formulations may be effective in decreasing agitation in emergency settings. Further investigations of the use of oral formulations – including the tablet forms – of atypical antipsychotics in the emergency treatment of agitation are warranted.*** (*Int J Psych Clin Pract* 2003; **7:** 217–221)

Keywords
acute agitation *atypical antipsychotics* *oral formulations*

INTRODUCTION

Agitation is very common, but until recently has received surprisingly little attention in psychiatric research. Recent efforts focused on the reduction of chemical and physical restraints in order to provide a more patient-centered management policy for agitation.

This prompted investigators/clinicians to search for novel treatment approaches with improved efficacy/safety profiles.[1] After atypical antipsychotics had been introduced, these agents became candidates for such an improved treatment approach for agitation first, in chronic and then in acute conditions. Some of these agents have proved to be efficacious in treating acute agitation in injectable formulations.[2–6] However, since one of the goals of a better treatment approach is to reduce the use of chemical and physical restraints and to provide a more patient-centered management policy, investigators/clinicians need to find out the least aggressive but effective treatment strategy for agitation.

Based on this need, we planned to conduct a randomized clinical trial comparing the effectiveness/safety of an oral atypical antipsychotic with an injectable classical antipsychotic for the treatment of acute agitation in emergency settings. However, before conducting a randomized well-powered study, first we completed an observational feasibility study to investigate the calming effect of risperidone in patients with acute agitation. While our randomized trial is currently under way, here we report the findings of the pilot study.

METHOD

Eighteen adult psychiatric patients who presented to the Emergency Department at the Massachusetts General Hospi-

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tal (MGH) with acute agitation were given either risperidone, 1–2-mg tablet, or haloperidol, 2–5 mg intramuscular (i.m.), depending on the decision of the acute psychiatry service (APS) physician and their preference of oral versus i.m. treatment. Concomitant use of lorazepam 1–2 mg per oral (p.o.) or i.m. was allowed during the study.

Personal and family histories as well as the information from the previous hospital records/charts were obtained, and diagnoses were made according to DSM-IV. Patients were evaluated at baseline as well as 60 and 120 min after the administration of the medication, using the Brief Psychiatric Rating Scale (BPRS, 18 items), the Brief Agitation Rating Scale (BARS, 10 items), the Agitated Behavior Rating Scale (ABRS, 14 items), and the Overt Agitation Severity Scale (OASS, 12 items). An overall side effect scale consisting of 16 items (orthostatic hypotension; dry mouth/nose; blurred vision; constipation; urinary retention; mydriasis; nausea/vomiting; acute dystonia; acute akathisia; seizure; sedation; changes in electrocardiogram/arrhythmia; dermatological side effects; jaundice; impotence/anorgasmia/decreased libido; neuroleptic malignant syndrome) had been created, with each item scaled from 0 to 3. Two study psychiatrists who were trained in the rating instruments and had no influence on the treatment decisions of the APS physician made all the efficacy ratings and side effect assessments whenever the patient gave verbal consent for such an evaluation. Only patients who were treated with risperidone tablets or i.m. haloperidol and gave verbal consent for the assessment of their agitation for 2 h are included in the study. The MGH Institutional Review Board approved the study.

RESULTS

Diagnostic and demographic characteristics of the 18 patients enrolled in the study are shown in Table 1a. Eight out of 10 patients in the haloperidol group were given concomitant lorazepam 1–2 mg (seven i.m.; one p.o.), while in the risperidone group, one out of eight patients was given concomitant lorazepam 1 mg p.o. during the study.

Individual data on the agitation scores at the baseline and study end point are provided for both groups in Table 1b. Results of the Wilcoxon Signed Ranks Test (paired samples) confirmed the hypothesis that both groups improve over time on all the rating instruments. In the risperidone group, the end point scores for the BPRS ($Z = 2.52$; $P = 0.012$), BARS ($Z = 2.52$; $P = 0.012$), ABRS ($Z = 2.52$; $P = 0.012$), and OASS ($Z = 2.52$; $P = 0.012$) are found to be significantly lower than the corresponding baseline scores. These values in the haloperidol group were statistically significant as well (BPRS ($Z = 2.81$; $P = 0.005$), BARS ($Z = 2.67$; $P = 0.008$), ABRS ($Z = 2.67$; $P = 0.008$), OASS ($Z = 2.67$; $P = 0.008$)).

The last observation carried forward an analysis of the mean improvement rates across the treatment groups and showed no significant differences in the BPRS, BARS, ABRS, and OASS between risperidone p.o. and haloperidol i.m. (Table 2). Two risperidone-treated patients (25%) and three haloperidol-treated patients (30%) needed repeated dosing at 60 min. Two risperidone-treated patients (one patient experienced dry mouth and sedation, one patient sedation), seven haloperidol-treated patients (one patient experienced dry mouth and sedation, six patients sedation) reported side effects.

DISCUSSION

These preliminary data suggest the effectiveness of risperidone in tablet form, at least in a subgroup of agitated psychiatric patients. In this study women preferred oral treatment. This is in contrast to the other risperidone study with men favoring oral treatment.[7] At present, we do not know the effects of the sex of the patients on the presentation of and/or treatment response of agitation. However, in two studies it was reported that the sex of the patient had no effect on treatment response to acute agitation.[7,8]

Concomitant use of lorazepam was allowed for both study groups as the APS physician judged to be needed. This resulted in a non-homogeneity of the study groups in terms of the number of subjects who were given the combination treatment, which may have influenced the results. Eighty percent of the patients in the haloperidol group, compared to 12.5% of the patients in the risperidone group, were given additional lorazepam. However, the baseline agitation scores of both groups were comparable. Thus, one may consider that any inflation on the improvement rates across the groups, if any exists, would be in favor of the haloperidol group. Nevertheless, underpowering of the study does not permit the drawing of a definitive conclusion on the effect of concamittant lorazepam use on the improvement rates of the study groups. Of note, considering the contribution of GABAergic (γ-aminobutyric acid) transmission to agitation in certain situations, concomitant use of lorazepam – as needed – may indeed be a reasonable strategy in treating agitation.[9]

There are four other efficacy trials of atypical antipsychotics on the treatment of acute agitation.[2,3,5,7,10] Among these, only one study rendered an atypical antipsychotic agent in oral formulation.[7] In this report, Currier and Simpson stated that a substantial number of patients who are in an emergency setting and would otherwise have received i.m. medications were indeed willing to accept an oral alternative.[7] In that study, risperidone liquid concentrate in combination with lorazepam p.o. was found to be as effective as the combination of haloperidol i.m. plus lorazepam i.m.[7] While the results of that study are entirely consistent with our observations, here we report preliminary data for the risperidone in tablet form in controlling agitation.

Recent trends in management of acute agitation require patient participation in planning and conduct of treatment.[1] In this context, agitated patients should be offered an active choice in their treatment on a menu of reasonable choices

Table 1a
Demographic and diagnostic features of the patients

Characteristics	*Risperidone (n = 8) (p.o.)*	*Haloperidol (n = 10) (i.m.)*	*P value*
Sex			
Male	1	8	
Female	7	2	
Age, Mean ± SD	39.25 ± 8.53	30.6 ± 9.96	0.1
DSM-IV diagnosis			
Bipolar illness–manic state	3	4	
Unip. depress.–depressive state	3	3	
Psychosis NOS	1	1	
Schizophrenia	1	1	
Borderline PD	–	1	
Mean baseline ratings			
BPRS	69.75 ± 18.75	63.60 ± 15.18	0.374
BARS	25.88 ± 6.77	29.60 ± 8.49	0.166
ABRS	40.00 ± 11.67	45.10 ± 11.06	0.196
OASS	42.25 ± 22.59	57.90 ± 27.12	0.182
Psychotic/nonpsychotic	4/4	4/6	0.680
Use of restraints	2/8	8/10	0.023

SD, standard deviation; BPRS, Brief Psychiatric Rating Scale; BARS, Brief Agitation Rating Scale; ABRS, Agitated Behavior Rating Scale; OASS, Overt Agitation Severity Scale; Unip. Depress., unipolar depression; Borderline PD, borderline personality disorder.

Table 1b
Individual data on the agitation scores at the baseline and end point

	Baseline scores				*End point scores*			
Patient initials	*BPRS*	*BARS*	*ABRS*	*OASS*	*BPRS*	*BARS*	*ABRS*	*OASS*
Risperidone								
HW	102	24	46	50	31	11	17	0
GL	62	27	48	46	21	12	18	2
DM	78	27	44	65	36	12	17	6
LLJ	79	36	50	71	23	10	17	1
MN	67	31	44	29	39	12	20	8
JP	45	17	24	25	30	10	14	0
AG	78	29	45	50	30	11	16	2
PS	47	16	19	2	31	11	15	0
Haloperidol								
LB	57	27	45	57	18	10	14	0
JV	43	10	18	0	38	10	18	0
FC	84	37	51	57	46	16	23	12
FL	58	37	53	70	27	13	21	7
LT	55	31	55	88	23	11	15	2
PB	58	37	53	60	26	20	24	19
TM	93	22	36	33	72	14	22	21
EC	73	28	50	45	55	21	14	30
JS	61	33	44	83	31	13	20	23
JP	54	34	46	86	39	13	15	21

BPRS, Brief Psychiatric Rating Scale; BARS, Brief Agitation Rating Scale; ABRS, Agitated Behavior Rating Scale; OASS, Overt Agitation Severity Scale.

Table 2
Improvement rates across the study groups on the agitation rating scales

	Change in score at the end point (LOCF) (Mean ± SD)		*Mann–Whitney* U	
Rating scale	*Risperidone (n = 8) (p.o.)*	*Haloperidol (n = 10) (i.m.)*	U	P *value*
BPRS	39.63 ± 19.38	26.10 ± 10.94	22.5	0.120
BARS	14.75 ± 6.69	15.50 ± 7.79	31.5	0.449
ABRS	23.25 ± 10.47	26.50 ± 11.63	29.5	0.349
OASS	39.88 ± 22.27	44.40 ± 27.49	36.0	0.722

SD, standard deviation; LOCF, last observation carried forward; BPRS, Brief Psychiatric Rating Scale; BARS, Brief Agitation Rating Scale; ABRS, Agitated Behavior Rating Scale; OASS, Overt Agitation Severity Scale.

including the tablet, liquid, as well as intramuscular formulations of various anti-agitation drugs. Such a therapeutic alliance may itself have an alleviating effect on agitation, in view of the dynamics of agitation by suggesting an internal, rather than an external locus of control.[1,11,12] Inclusion of the oral formulations among the treatment choices for acute agitation is further supported by the prior studies indicating comparable efficacy of oral medications to the i.m. ones.[7,8,13–15]

Atypical agents such as risperidone, ziprasidone, and olanzapine, possibly because of their activities on the dopaminergic, serotonergic, and histaminergic receptors, may possess a rapid positive effect in decreasing agitation and aggression in psychiatric patients [2,3,5,9]. Thus, these agents should be included on the menu of reasonable choices with oral, liquid, and i.m. formulations, provided that controlled clinical data support their efficacy. In addition to their superior side effect profiles, use of these agents in the emergency treatment of agitation offers a pharmacological continuum for the subsequent care of the patient.[16]

This preliminary pilot study has important limitations regarding generalizability. These include the small sample size, the use of a nonrandomized open design, and hence, some potential for a selection bias. Nonetheless, this pilot study has been conducted as a feasibility study; and by providing background data, warrants further investigation of the oral atypical antipsychotic agents in the treatment of acute agitation with randomized designs.

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KEY POINTS

- Recent trends in management of acute agitation require patient participation in planning and conduct of treatment
- In this context, agitated patients should be offered an active choice in their treatment on a menu of reasonable choices including tablet, liquid, as well as intramuscular formulations of various anti-agitation drugs
- These preliminary data suggest the effectiveness of risperidone in tablet form, at least in a subgroup of agitated psychiatric patients

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