The Comparative Peripheral Anticholinergic-Like Adverse Event Profiles of Olanzapine and Risperidone

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Objective: To test the hypothesis that reported in vitro muscarinic receptor affinity differences between olanzapine and risperidone would be reflected in peripheral solicited anticholinergic adverse event frequencies.

Method: Data from a double-blind, randomized trial of olanzapine versus risperidone in 339 patients (age range, 18–65 years) with DSM-IV schizophrenia spectrum acute psychosis were retrospectively analyzed. Subgroups based on the median of the mean daily drug dose were constructed (olanzapine ≤ 17 mg; olanzapine > 17 mg; risperidone ≤ 6 mg; risperidone > 6 mg). Mean daily dose of adjunctive anticholinergic medication was compared using ANOVA, and frequencies of treatment-emergent solicited adverse events defined by the Association de Méthodologie et de Documentation en Psychiatrie (AMDP-5) were analyzed using categorical methods.

Results: Mean daily anticholinergic dose was significantly higher overall for the risperidone group (0.68 ± 1.27 mg) than for the olanzapine group (0.27 ± 0.76 mg) ($p = .002$). When only patients who did not receive anticholinergic adjunct therapy were considered, no significant differences in the frequency of specific anticholinergic adverse events occurred in olanzapine-treated patients as compared with risperidone-treated patients ($p \geq .245$). There was also no significant difference between olanzapine and risperidone in the frequency of any anticholinergic adverse event ($p = .458$).

Conclusion: At clinically effective doses, olanzapine and risperidone did not differ significantly in frequency of peripheral anticholinergic events. These results support the view that, for olanzapine and risperidone, in vitro anticholinergic receptor binding (K_i values) may not predict in vivo peripheral events.

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Olanzapine was originally reported, based on in vitro characterization, to have potent binding affinity at the muscarinic receptors, subtypes M_1 through M_5,[1] and no direct interaction with the nicotinic receptor system.[2–5] However, evidence from ex vivo binding, in vivo binding, and in vivo function in animals suggests that olanzapine has minimal anticholinergic effects.[6–8] Consistent with the animal data, peripheral anticholinergic adverse events in humans potentially attributable to olanzapine treatment (i.e., visual accommodation disturbances, constipation, increased heart rate, and dry mouth) when measured in double-blind, placebo-controlled trials occurred at rates that were relatively low[9] in comparison with rates expected from the originally reported in vitro muscarinic receptor characterizations. These data are further supported by Chengappa et al.,[10] who suggest that olanzapine in vivo (patient-reported adverse events) is much less anticholinergic than would have been predicted from the originally published in vitro data.[2,6,11]

The objective of the present analysis was to characterize the extent of olanzapine's in vivo anticholinergic activity by comparing solicited anticholinergic treatment-emergent adverse events as reported in a randomized, double-blind clinical trial of olanzapine and risperidone in patients not taking adjunctive anticholinergic medication. Risperidone was specifically selected owing to the expectation, based on in vitro assay data, that this commonly used agent had very low in vivo (in humans) affinity for muscarinic receptors.[6,11] The hypothesis tested was whether olanzapine and risperidone differed substantially in clinical, peripheral, anticholinergic-associated adverse events as indexed by the Association de Méthodologie et de Documentation en Psychiatrie (AMDP-5)–solicited adverse event symptom list.

METHOD

Data from 339 study subjects (aged 18–65 years; mean ± SD = 36.21 ± 10.73 years) with DSM-IV–diagnosed schizophrenia, schizophreniform disorder, or schizoaffective disorder who participated as outpatients in a previously reported[12] 28-week, international, multicenter, double-blind, randomized, flexible-dosing comparative trial of risperidone (4–12 mg/day) and olanza-

Table 1. Mean Daily Antipsychotic and Anticholinergic Dose

Therapy	Sample Size (N)	Daily Antipsychotic Dose (mg) Mean	SD	Daily Anticholinergic Dose (mg)[a] Mean	SD
Olanzapine	170	16.7	3.1	0.27	0.76[b]
≤ 17 mg	81	13.9	2.2	0.17	0.60[c]
> 17 mg	89	19.2	0.7	0.35	0.87
Risperidone	165	6.8	2.2	0.68	1.27
≤ 6 mg	74	4.9	1.1	0.76	1.43[d]
> 6 mg	91	8.4	1.5	0.61	1.13

[a]Mean daily anticholinergic dose was converted to benztropine equivalents.
[b]Risperidone required statistically significantly higher (p = .002) mean anticholinergic dose than olanzapine (Type III sums of squares p value for ranked data).
[c]Mean daily anticholinergic dose was not significantly different (p = .085) between olanzapine ≤ 17 mg and > 17 mg.
[d]Mean daily anticholinergic dose was not significantly different (p = .418) between risperidone ≤ 6 mg and > 6 mg.

Table 2. Number (%) of Patients Requiring at Least 1 Dose of Anticholinergic Medication

Therapy	Sample Size (N)	No	Yes	%
Olanzapine	170	136	34	20.0[a]
≤ 17 mg	81	70	11	13.6[b]
> 17 mg	89	66	23	25.8[c]
Risperidone	165	110	55	33.3
≤ 6 mg	74	53	21	28.4
> 6 mg	91	57	34	37.4

[a]The percentage of patients requiring at least 1 dose of anticholinergic medicine was statistically higher (p = .006) in the risperidone group than the olanzapine group.
[b]The percentage of risperidone ≤ 6-mg patients requiring at least 1 dose of anticholinergic medicine was statistically higher (p = .023) than olanzapine ≤ 17-mg patients.
[c]The percentage of risperidone > 6-mg patients requiring at least 1 dose of anticholinergic medicine was not statistically different (p = .097) from olanzapine > 17-mg patients.

pine (10–20 mg/day) were included in this post hoc analysis. Of the 339 patients, 335 had evaluable dosing data. Treatment-related subgroups were constructed for comparison purposes using mean daily dosing. For risperidone, the 2 groups were ≤ 6 mg/day and > 6 mg/day, and for olanzapine, the 2 groups were ≤ 17 mg/day and > 17 mg/day.

Specific requirements for use of adjunctive anticholinergic treatment for this analysis are described by Tran et al.[12] The use of anticholinergic medication as prophylaxis for extrapyramidal symptoms was prohibited. To characterize the use of anticholinergic medications during the study, the mean daily anticholinergic dose used by any patient was standardized to benztropine equivalents (expressed in mg/day), applying an accepted conversion table method.[13]

To characterize the presence or absence of peripheral anticholinergic treatment-emergent adverse events (defined as adverse events occurring with greater severity than at the placebo baseline visit), the inquiry system developed by the AMDP-5 was employed. At each study visit, the investigator solicited the severity with which the subject experienced a list of events, of which 4 were selected for this report as presumably anticholinergic: dry mouth, constipation, blurred vision, and micturition difficulties.

Statistical Analysis

The analyses reported here include all patients and, separately, only the subset of subjects from the previously reported Tran et al. study[12] who did not receive any adjunctive anticholinergic agents after the baseline visit. Mean dose of anticholinergic medication was analyzed using analyses of variance. Frequency of treatment-emergent solicited adverse events and frequency of benztropine use were analyzed using chi-square tests (or Fisher exact test in the case of small cell frequencies). All tests were 2-tailed with $\alpha = .05$.

RESULTS

The mean daily dose of risperidone (≤ 6 mg/day or > 6 mg/day) and olanzapine (≤ 17 mg/day and > 17 mg/day) and their corresponding mean daily anticholinergic dose expressed in benztropine equivalents are summarized in Table 1. Mean daily dose of anticholinergic medication was significantly higher overall for the combined risperidone group (0.68 ± 1.27 mg) than for the combined olanzapine group (0.27 ± 0.76 mg) (p = .002).

The mean daily dose of anticholinergic medication was not significantly different between risperidone ≤ 6 mg/day and > 6 mg/day (p = .418). Similarly, the mean daily dose of anticholinergic use was not significantly different between olanzapine ≤ 17 mg/day or > 17 mg/day (p = .085). The percentage of patients requiring at least 1 dose of anticholinergic medicine was statistically higher (p = .006) in the risperidone group than the olanzapine group (Table 2).

Among the group who did not receive anticholinergic therapy during the trial, there were no significant differences in the frequency of anticholinergic events occurring in olanzapine-treated patients as compared with risperidone-treated patients (p ≥ .245). Among patients not taking concomitant anticholinergic medications, the percentage of patients with anticholinergic AMDP-5–solicited treatment-emergent events is summarized in Table 3. The percentage of patients reporting any of the 4 solicited events was not statistically different (p = .525) with olanzapine (30.1% ± 7.8%) as compared with risperidone (34.6% ± 8.9%).

DISCUSSION

Data from this analysis suggest that olanzapine has relatively little clinical interaction with muscarinic receptors in vivo and olanzapine is not more significantly peripherally anticholinergic in vivo than risperidone. This is

Table 3. Number of Patients (%) With AMDP-5–Solicited Treatment-Emergent Anticholinergic Events Among Patients Not Taking Anticholinergic Agents[a]

	Olanzapine						Risperidone						
	All (N = 133)		≤ 17 (N = 67)		> 17 (N = 66)		All (N = 110)		≤ 6 (N = 53)		> 6 (N = 57)		
Event	N	%	N	%	N	%	N	%	N	%	N	%	p Value[b]
Dry mouth	27	20.3	17	25.4	10	15.2	21	19.1	13	24.5	8	14.0	0.245
Constipation	11	8.3	3	4.5	8	12.1	12	10.9	5	9.4	7	12.3	0.389
Blurred vision	14	10.5	8	11.9	6	9.1	17	15.4	9	17.0	8	14.0	0.621
Micturition difficulties	5	3.8	1	1.5	4	6.1	7	6.4	3	5.7	4	7.0	0.483
Any event[c]	40	30.1	22	32.8	18	27.3	38	34.6	21	39.6	17	29.8	0.525

[a]No significant differences among 4 dose groups.
[b]Chi-square test among 4 groups.
[c]At least 1 report of dry mouth, constipation, blurred vision, or micturition difficulties.

consistent with recent in vivo binding and in vivo functional studies in animals that demonstrate relatively low levels of anticholinergic activity for olanzapine.[6–8] Further, the results of the present analysis are also consistent with those reported by Street et al.[14] of peripheral anticholinergic events in a placebo-controlled dose-finding study of 5, 10, and 15 mg/day of olanzapine in Alzheimer's disease patients with psychosis and/or agitation. The Street et al.[14] study demonstrated that no single event at any dose of olanzapine was present significantly more often than in the placebo-treated group. These events (amblyopia, constipation, dry mouth, dry skin, fecal impaction, fever, intestinal obstruction, tachycardia, urinary retention, and vasodilation) included objectively observable occurrences in this cognitively impaired population.

Although Tran et al.[12] reported that risperidone patients require more frequent dosing of anticholinergic agents compared with olanzapine patients, it has been suggested that, in that analysis, this difference was primarily attributable to the receipt of dosages > 6 mg/day by some risperidone patients. In the present study, though, risperidone patients taking ≤ 6 mg/day had similar anticholinergic use compared with those taking > 6 mg/day. The more frequent anticholinergic use among risperidone patients reported by Bymaster and Falcone[15] has also been interpreted to mean that risperidone has less anticholinergic activity than olanzapine in vivo simply because more anticholinergic drug is required by risperidone patients. This interpretation takes into account the fact that anticholinergic medications are given to control extrapyramidal symptoms (EPS). If a drug such as olanzapine has a favorable EPS profile because of its intrinsic anticholinergic activity, expected anticholinergic use would be correspondingly low, as seen with olanzapine use. However, such an interpretation if correct would have been expected to be most evident in comparison with solicited events in those patients not taking any adjunct anticholinergic agents who were assigned to the high-dose olanzapine group (> 17 mg/day) versus low-dose risperidone group (≤ 6 mg/day). In fact, this was not seen as outlined in Table 3 where the total percentage of patients reporting any event on olanzapine > 17 mg/day was 27.3% versus 39.6% on risperidone ≤ 6 mg/day. However, because the flexible-dose design of the original study requires that comparisons between high- and low-dose groups performed post hoc be made with caution and any inferences drawn should be interpreted as descriptive, still it is reasonable to consider that if a drug is significantly anticholinergic in vivo it could be expected to demonstrate a direct relationship between higher dosages of the drug and more frequent reporting of anticholinergic events.

In this analysis, with patients receiving adjunctive anticholinergic medication excluded from the study population, the overall incidence of peripheral anticholinergic effects seen with risperidone was comparable with that seen with olanzapine. This raises the question of whether some previously published in vitro muscarinic inhibition constants (K_i values) are instructive when it comes to predicting the in vivo peripheral effects in patients at clinically effective doses. There are several possible explanations for this finding. First, the AMDP-5 might be insensitive to anticholinergic effects. A second potential concern is that this analysis was underpowered for such post hoc comparisons. However, when patients taking anticholinergic medications were included in the analysis, a significant difference in blurred vision (favoring olanzapine) was noted between treatment groups, indicating that differences in the presence of these 4 complaints that are associated with anticholinergic activity of medicines could be detected by the AMDP-5. Furthermore, a power analysis suggests that this study was adequately powered (80%) to detect a relative risk of 2.1 or more in overall adverse event frequencies between the 2 compounds.

A third explanation for the lack of a difference revolves around the reported in vitro receptor antagonist profiles of olanzapine and risperidone. In this regard, 4 points are noteworthy: first, it has recently been reported for both olanzapine and clozapine that interactions with muscarinic receptors are dependent in vitro on the conditions under which binding is assessed and that these interactions may

have been grossly overestimated in some receptor-binding experiments due to nonphysiologic conditions.[15] Second, an in vitro pharmacologic difference between olanzapine and risperidone is that risperidone has 5-hydroxytryptamine $(5\text{-HT})_{2A}$ antagonist properties that are 10-times greater in vitro than for olanzapine.[6] This is potentially relevant since 5-HT_{2A} antagonists have been suggested to diminish the release of acetylcholine from cholinergic nerves.[16] However, the relevance of this finding to the study's results is somewhat equivocal since ritanserin, a potent 5-HT_{2A} antagonist, has been only sporadically reported in clinical trials to produce anticholinergic-like effects (i.e., dry mouth, constipation, blurred vision, and urinary problems).[17] Third, olanzapine's most potent receptor antagonist property is its blockade of the 5-HT_6 receptor, a receptor that risperidone could be anticipated to block in vivo only very weakly, if at all, at purported optimal dosages ≤ 6 mg/day.[18] In rodents, atropine has been demonstrated to reverse the effects of 5-HT_6 receptor antagonism, an observation that indicates that the 5-HT_6 receptor may have an important indirect regulatory role in the functioning of the cholinergic system.[19] Thus, while speculative, it is possible that olanzapine 5-HT_6 antagonism accounts for the observations of the equality with risperidone in this study. Fourth, it has long been recognized that events such as dry mouth, constipation, blurred vision, micturition difficulties, and increased heart rate (tachycardia) may arise via mechanisms that bear no direct relationship to the cholinergic system or the presence or absence of anticholinergic activity of medicines.[20–22] Therefore, it is likely that the events noted here are best termed *anticholinergic-like* rather than anticholinergic and in that regard, olanzapine and risperidone appear to be highly similar in vivo.

Post hoc analyses are not a full substitute for prospective, randomized, double-blind, placebo-controlled, replicated clinical trials. This analysis has several limitations, among which is the lack of a placebo control; whereas in placebo-controlled trials, placebo-, olanzapine-, and risperidone-treated patients all report the occurrence of these events to varying degrees. Therefore, it is not possible to conclude at present from a comparative perspective that either risperidone or olanzapine are equal to placebo in anticholinergic effects. In fact, the data received by the U.S. Food and Drug Administration for approval of these 2 different agents allowed the conclusion that treatment-emergent anticholinergic-like events occurred more frequently in patients treated with olanzapine or risperidone than in patients treated with placebo. Here we report that the relative potential of each to produce these events appears to be equal.

CONCLUSION

A similar incidence of peripheral anticholinergic effects was seen with olanzapine as compared with risperidone among patients who received no adjunctive anticholinergic medication. This finding suggests that these compounds' published in vitro muscarinic K_i values may not be useful in predicting incidence of in vivo peripheral effects at clinically effective doses. The more frequent dosing of anticholinergic agents required by risperidone patients compared with olanzapine patients originally reported by Bymaster and Falcone[15] was not solely attributable to risperidone patients' taking dosages > 6 mg/day.

Drug names: atropine (Donnatal and others), benztropine (Cogentin and others), clozapine (Clozaril and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Kennedy JS, Kwentus J, Kumar V, et al. Cholinergic drugs in the treatment of Alzheimer's disease. In: Esidorfer C, Kumar V, eds. Advances in the Diagnosis and Treatment of Alzheimer's Disease. New York, NY: Springer Publishing Company; 1998
2. Bymaster FP, Rasmussen K, Calligaro DO, et al. In vitro and in vivo biochemistry of olanzapine: a novel, atypical antipsychotic drug. J Clin Psychiatry 1997;58(suppl 10):28–36
3. Bymaster FP, Nelson DL, DeLapp NW, et al. Antagonism by olanzapine of dopamine D1, serotonin 2, muscarinic, histamine H1 and alpha 1-adrenergic receptors in vitro. Schizophr Res 1999;37:107–122
4. Bartholini G. Interactions of striatal dopaminergic, cholinergic, and GABA-ergic neurons: relation to extrapyramidal function. Trends Pharmacol Sci 1980;1:138–140
5. Bolden C, Cusack B, Richelson E. Antagonism by antimuscarinic and neuroleptic compounds at the five cloned human muscarinic cholinergic receptors expressed in Chinese hamster ovary cells. J Pharmacol Clin Ther 1992;260:576–580
6. Schotte A, Janssen PFM, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology (Berl) 1996;124:57–73
7. Zhang W, Bymaster FP. The in vivo effects of olanzapine and other antipsychotic agents on receptor occupancy and antagonism of dopamine D_1, D_2, D_3, 5-HT_{2A} and muscarinic receptors. Psychopharmacology (Berl) 1999;141:267–278
8. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? a review of the evidence. Neuropsychopharmacology 1998;18:63–101
9. Beasley CM, Tollefson G, Tran P, et al. The Olanzapine HGAD Study Group: olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111–123
10. Chengappa KN, Pollock BG, Parepally H, et al. Anti-cholinergic differences among patients receiving standard clinical doses of Zyprexa or clozapine: a laboratory assay and clinical study [poster]. Presented at the 152nd annual meeting of the American Psychiatry Association; May 15–20, 1999; Washington, DC
11. Bymaster FP, Hemrick-Luecke SK, Perry KW, et al. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, α_1-adrenergic and muscarinic receptors in vivo in rats. Psychopharmacology (Berl) 1996;124:87–94
12. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
13. Tran PV, Dellva MA, Tollefson GD, et al. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. J Clin Psychiatry 1997;58:205–211. Correction 1997;58: 275
14. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer's disease in nursing care facilities: a double-blind, randomized trial. Arch Gen Psychiatry. In press
15. Bymaster FP, Falcone JF. Decreased binding affinity of olanzapine and clozapine for clonal human muscarinic receptor subtypes in intact CHO cells in physiological medium. Eur J Pharmacol 2000;390:245–248

16. Ramirez MJ, Cenarruzabeitia E, Lasheras B, et al. 5-HT_2 receptor regulation of acetylcholine release induced by dopaminergic stimulation in rat striatal slices. Brain Res 1997;757:17–23
17. Bakish D, Lapierre YD, Weinstein R, et al. Ritanserin, imipramine, and placebo in the treatment of dysthymic disorder. J Clin Psychopharmacol 1993;13:409–414
18. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
19. Sleight AJ, Boess FG, Bos M, et al. The putative 5-HT_6 receptor: localization and function. Ann N Y Acad Sci 1998;861:91–96
20. Bein HJ. Prejudices in pharmacology and pharmacotherapy: the so-called anticholinergic effect of antidepressants. Agent Actions 1977;7:313–315
21. Zyprexa [package insert]. Indianapolis, Ind: Eli Lilly and Company; 1997
22. Risperdal [package insert]. Titusville, NJ: Janssen Pharmaceutica Inc; 1999