Thyroid Function in Treatment-Resistant Schizophrenia Patients Treated With Quetiapine, Risperidone, or Fluphenazine

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Background: Thyroid dysfunction is relatively common in patients with schizophrenia, possibly related to a genetic linkage of the disorders and to antipsychotic treatment. Quetiapine has been implicated as causing some degree of thyroid function changes, yet it remains unclear as to what extent or why these changes may occur. Furthermore, the need for thyroid function monitoring in patients taking this medication is not definitive.

Method: Thyroid function was assessed in 38 adult DSM-IV–diagnosed schizophrenia patients after 6 weeks of prospective, double-blind, randomized treatment with quetiapine (400 mg/day), risperidone (4 mg/day), or fluphenazine (12.5 mg/day). Data were collected from 1997 to 2002.

Results: At baseline, the percentages of randomized patients with abnormal values were 18% (4/22) for serum T_3 resin uptake, 13% (4/30) for thyroid-stimulating hormone (TSH), and 9% (2/22) for total serum thyroxine (TT_4), representing fairly widespread thyroid abnormalities independent of treatment group. Little change was noted in thyroid function during the 6 weeks of treatment, except for a significant decrease in TT_4 values for those taking quetiapine ($p = .01$). Clinically, however, no patients demonstrated any signs or symptoms of hypothyroidism during the study, nor were any significant changes in the free thyroxine index or TSH levels noted.

Conclusions: It is expected that TT_4 levels will decrease during quetiapine treatment, and this may possibly be related to competitive metabolism of thyroid hormones and quetiapine by UDP-glucuronosyltransferase. Routine monitoring of thyroid function in quetiapine-treated patients without a history of thyroid disease is not recommended.

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Thyroid function abnormalities in people with schizophrenia were first reported in the 1960s in chronic patients treated with antipsychotic medications.[1] An increased prevalence of thyroid disorder has also been noted in families of individuals with schizophrenia, suggesting a possible genetic linkage to the illness. Recently, a gene mapped to Xq13 (HOPA) was found to be associated with hypothyroidism and schizophrenia, and polymorphisms of this HOPA gene have been significantly linked to both disorders, providing a genetic basis for the familial association of thyroid disease and schizophrenia.[2–5]

Some reports have noted that thyroid levels are elevated only in the acute phase of psychotic illness and decrease with clinical response to antipsychotics.[6–8] However, in chronic hospitalized patients (N = 189), abnormal thyroid tests are prevalent (> 36%). In most cases, patients with abnormal thyroid tests are found clinically to be euthyroid.[9] Endogenous dopamine is known to inhibit the stimulatory effects of thyroid-releasing hormone, and any drug with dopaminergic activity can inhibit thyroid-stimulating hormone (TSH) secretion.[10] Thus, it is not surprising that patients treated with conventional antipsy-

chotics will experience abnormal thyroid test results on the basis of the drugs' pharmacologic profile and dopaminergic activity.[11]

A few studies have identified that a blunted baseline TSH response has predicted a more favorable outcome.[8,12] Interestingly, clozapine as compared with haloperidol and control groups has demonstrated a blunted TSH response, most likely relating to its different pharmacologic profile and different dopaminergic actions.[13] The second-generation antipsychotics, as is the case with clozapine, have differing pharmacologic profiles as compared with the conventional antipsychotics; however, the effects of these medications on thyroid function have received little attention. Some attention has been paid to quetiapine, which has listed in its product labeling that free thyroxine (T_4) was noted to increase in a dose-related fashion and that 0.4% of patients treated in clinical trials had an elevation in TSH. Rarely, hyperthyroidism and goiter have also been reported in trials during quetiapine and olanzapine use.[14] While the majority of treatment guidelines and recommendations do not recommend routine thyroid function tests during antipsychotic treatment, there are advocates of routine monitoring.[15]

We conducted a randomized double-blind trial comparing the safety and efficacy of quetiapine, risperidone, and fluphenazine in treatment-resistant schizophrenia. Specifically, we report here the thyroid function during 6 weeks of treatment with these drugs. We are unaware of any published studies examining thyroid function during treatment with quetiapine compared with another second-generation antipsychotic (risperidone) and a conventional antipsychotic (fluphenazine).

METHOD

All subjects in the study were diagnosed as having schizophrenia according to DSM-IV criteria. Subjects in this study were all medically healthy and were considered treatment-resistant as evidenced by (1) persistent positive psychotic symptoms (score ≥ 4 [moderate] on at least 2 of 4 positive symptom items on the Brief Psychiatric Rating Scale [BPRS][16] [rated on a 1–7 scale]), (2) the current presence of at least moderately severe illness as rated by the total BPRS score (score ≥ 45 on the 18-item scale) and a score of ≥ 4 (moderate) on the Clinical Global Impressions scale,[17] (3) 2 failed historical trials of antipsychotics of at least 6 weeks' duration at doses of at least 600 mg/day of chlorpromazine equivalents, and (4) no stable period of good social or occupational functioning within the last 5 years. Subjects were treated with quetiapine at a fixed dose of 400 mg/day, risperidone at a fixed dose of 4 mg/day, or fluphenazine at a fixed dose of 12.5 mg/day for 12 weeks in a randomized double-blind trial that was preceded by a qualifying lead-in trial. The lead-in trial consisted of 4 to 6 weeks of monotherapy with conventional antipsychotics or, in a few cases, olanzapine. Efficacy results of this study have been presented elsewhere.[18] Data were collected from 1997 to 2002.

Blood was drawn in the morning at baseline and at week 6 following randomization for evaluation of thyroid function. Tests included total serum thyroxine (TT_4), free thyroxine index (FT_4I), serum T_3 resin uptake (T_3RU), and TSH. Not all subjects had all 4 levels reported; thus, all subjects included in this study were those who had complete baseline laboratory values and at least 1 of the 4 thyroid function tests completed following 6 weeks of treatment.

Specific thyroid status or function can be categorized by tests that measure the concentration of products secreted by the thyroid gland, evaluate the integrity of the hypothalamic-pituitary axis, assess inherent thyroid gland function, or detect antibodies to thyroid tissue. Tests that directly or indirectly measure the concentration of T_4 and T_3 include the FT_4I, the TT_4, and the T_3RU. Serum T_3 resin uptake is often used to verify the clinical significance of measures of serum TT_4 or TT_3 levels because it is an indicator of thyroid-binding, protein-induced alterations of the measurements. FT_4I provides an index of free thyroxine levels and adjusts for the effects of alterations in thyroid-binding protein on the TT_4 assay and is thus one of the most useful parameters of the thyrometabolic state currently available. TSH is a useful test to confirm a diagnosis of hypothyroidism. Thus, the general guidelines for diagnosis of primary hypothyroidism are a low FT_4I level and an elevated TSH level. The presence of low FT_4I and normal or low serum TSH levels is also indicative of secondary hypothyroidism. Therefore, FT_4I, TSH, TT_4, and T_3RU measurements, as used in this study, provide adequate physiologic measures to detect changes in thyroid function and to characterize hypothyroidism (along with associated symptoms).[10] Serum T_3 uptake and TT_4 were both assayed using the CEDIA (cloned enzyme donor immunoassay) technology (Microgenics Corporation, Freemont, Calif.) with the genetically engineered bacterial enzyme β-galactosidase. TSH was measured by a 2-site sandwich immunoassay using direct chemiluminometric technology (ADVIA Centaur, Bayer HealthCare LLC, Tarrytown, N.Y.). FT_4I is the product obtained by multiplication of the TT_4 value by the T_3RU value.

Routine concomitant medications with primary central nervous system activity were not permitted in this protocol except for specified p.r.n. doses of lorazepam and benztropine that were permitted for agitation, anxiety, and extrapyramidal symptoms. No subjects were given scheduled doses or treated chronically with lorazepam or benztropine. The use of other medications was limited to a list of a few classes of medications with little potential for metabolic interactions, such as oral hypoglycemics, laxatives, diuretics, nonsteroidal anti-inflammatory agents, antibiotics (excluding macrolids and rifampin), and lim-

ited use of antihypertensives (excluding calcium channel blockers, guanfacine, clonidine, reserpine, and methyldopa). This study was approved by the University of Maryland and the State of Maryland Institutional Review Boards. All subjects were considered able to consent by use of the Evaluation to Sign Consent,[19] and all subjects signed consent statements before research participation.

Baseline and endpoint demographic and clinical characteristics were compared using the Kruskal-Wallis exact test for continuous data. Pearson χ^2 and Fisher exact tests were used to examine dichotomous variables. Paired 2-tailed t tests were used for within-group changes, and significance was defined as an $\alpha < .05$.

RESULTS

Thirty-eight subjects were randomly assigned to treatment with risperidone, quetiapine, or fluphenazine. Thirty patients (79%) had all 4 thyroid function tests completed at baseline and at least 1 of the 4 tests completed during the 6-week study (N = 10, quetiapine; N = 11, risperidone; and N = 9, fluphenazine). The demographic information for the groups is listed in Table 1. There were no significant differences noted between drug groups.

At baseline, 18% (4/22) of randomized patients had abnormal serum T_3RU values. Thirteen percent (4/30) of subjects had abnormal TSH values, and 9% (2/22) had abnormal TT_4 values. Table 2 shows the number of subjects with abnormal thyroid laboratory values at baseline and endpoint for each randomized medication group. At baseline there were no significant differences among drug groups in any thyroid functioning test. Table 3 shows the change in mean laboratory values of thyroid function following 6 weeks of antipsychotic treatment. Mean TT_4 levels decreased significantly from baseline during quetiapine treatment ($t = -3.93$, $p = .01$), which also represented a significant between-group change for this level (Kruskal-Wallis exact test; $\chi^2 = 8.00$, $df = 2$, $p = .01$). Clinically, no patients demonstrated any signs or symptoms of hypothyroidism during the study.

Table 1. Demographic Information for 30 Schizophrenia Patients Treated With Quetiapine, Risperidone, or Fluphenazine

Variable	Quetiapine (N = 10)	Risperidone (N = 11)	Fluphenazine (N = 9)
Age, mean ± SD, y	42.6 ± 5.8	45.3 ± 9.2	43.6 ± 7.6
Race, N (%)			
Black	6 (60)	7 (64)	5 (56)
White	4 (40)	4 (36)	4 (44)
Sex, N (%)			
Males	8 (80)	7 (64)	7 (78)

DISCUSSION

It is common for people with chronic schizophrenia to exhibit abnormal laboratory values for thyroid function tests. Whether this is related to the underlying etiology of schizophrenia, or the effects of stress, state of the illness, or drug treatment remains unknown. In our study, at baseline, approximately 1 in 6 patients had an abnormal value in 1 or more of the thyroid function tests. This prevalence is lower than other reported findings where 36% of all people chronically hospitalized for schizophrenia had thyroid test result abnormalities,[9] but still indicates that those with schizophrenia are a clinically important subgroup of patients.

In clinical trials and in product labeling for quetiapine, it is reported that treatment is often associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. However, in the clinical trials of this drug, no notable changes were observed in TSH levels for most people; only 0.4% (10/2386) experienced significant increases in TSH levels.[14] In the published literature, only 1 case is reported of hypothyroidism associated with quetiapine use.[20] Moreover, this patient had a history of radioactive iodine treatment for previous hyperthyroidism and thus had a predisposed sensitivity to thyroid problems. Quetiapine-treated patients in our study had significant decreases in TT_4 levels, yet mean FT_4I levels did not significantly decrease, nor were there increases in TSH levels. This finding is similar to others who have reported decreases in T_4 in both euthyroid adolescents and the elderly.[21,22] In fact, the FT_4I provides a more accurate reflection of free thyroxine by adjusting for the effect of alterations in thyroid-binding proteins on the assay. These alterations of FT_4I and TSH are also more clinically indicative of hypothyroidism than is TT_4, and levels of FT_4I and TSH did not appear to indicate the occurrence of primary or secondary hypothyroidism.[10] Thus, it does not appear that hypothyroidism is a major problem with quetiapine, and routine monitoring of thyroid function does not appear to be warranted in people without a history of thyroid disease.

A few explanations are possible, however, for the thyroid changes we observed in the study for quetiapine. There is new evidence that UDP-glucuronosyltransferase (UGT) is responsible for the glucuronidation of both thyroid hormones and certain psychotropic medications.[23] As compared with phase 1 metabolism by cytochrome P450 isoenzymes, phase 2 glucuronidation by means of the UGT enzymes has received little attention. Until recently it was difficult to develop analytic methods to measure glucuronides, but current work has now shown that at least 24 different UGT human genes have been identified and are classified into 2 families (UGT1 and UGT2) on the basis of sequence homology. The UGT1A4 enzyme specifically is known to metabolize cyclic tertiary amines such as piperidines and piperazines. Thus, antipsychotics such as clozapine, loxapine, chlorpromazine, and olanzapine are all piperazine-containing drugs that undergo

Table 2. Abnormal Laboratory Values for Thyroid Function Tests at Baseline and Endpoint for 30 Schizophrenia Patients Treated With Quetiapine, Risperidone, or Fluphenazine[a]

	Quetiapine (N = 10)				Risperidone (N = 11)				Fluphenazine (N = 9)			
	Baseline		Endpoint		Baseline		Endpoint		Baseline		Endpoint	
Test (reference range)	N/N	%	N/N	%	N/N	%	N/N	%	N/N	%	N/N	%
Total serum thyroxine (5–12 μg/dL)	1/6 (H)	17	2/6 (L)	33[b]	1/8 (H)	13	1/8 (H)	13	0/8	0	0/8	0
Free thyroxine index (0.9–2.3 ng/dL)	0/5	0	0/6	0	0/6	0	0/8	0	0/8	0	0/8	0
Serum T_3 resin uptake (25%–35%)	0/6	0	1/6 (H)	17[b]	2/8 (1L,1H)	25	3/8 (1L,2H)	38[b]	2/8 (H)	25	2/8 (H)	25
Thyroid-stimulating hormone (0.5–5.0 μIU/mL)	2/10 (1L,1H)	20	2/10 (L)	20[b]	1/11	9	0/11	0	1/9 (L)	11	3/9 (1H,2L)	33[b]

[a]Not all patients had all thyroid function tests completed. Thus, the percentage reflects that of the total values present for that group.
[b]The percentage of subjects with abnormal values changed since baseline.
Abbreviations: H = high (laboratory value was abnormally high), L = low (laboratory value was abnormally low).

Table 3. Change in Thyroid Function Test Results (baseline to endpoint) for 30 Schizophrenia Patients Treated With Quetiapine, Risperidone, or Fluphenazine

Test (reference range)	Quetiapine (N = 10), Mean ± SD Change	Risperidone (N = 11), Mean ± SD Change	Fluphenazine (N = 9), Mean ± SD change	Significance Among Drugs
Total serum thyroxine (5–12 μg/dL)	–2.37 ± 1.48[a]	–0.01 ± 1.02	0.62 ± 1.91	p = .01[b]
Free thyroxine index (0.9–2.3 ng/dL)	–0.76 ± 0.68	–0.07 ± 0.48	0.22 ± 0.62	Not significant
Serum T_3 resin uptake (25%–35%)	–0.00 ± 2.76	0.38 ± 1.92	0.30 ± 1.36	Not significant
Thyroid-stimulating hormone (0.5–5.0 μIU/mL)	–0.86 ± 1.60	–0.28 ± 1.05	–0.49 ± 1.68	Not significant

[a]Baseline to endpoint change within drug group (paired t tests) ($t = -3.93$, $p = .01$).
[b]Significance among drug groups (Kruskal-Wallis exact test) ($\chi^2 = 8.00$, $df = 2$, $p = .01$).

N-glucuronidation by UGT1A4.[24–26] Recently, it was reported that many agents do compete for the glucuronidation of olanzapine, representing a possibility for drug-drug interactions through this pathway.[27] Interestingly, other recent findings have suggested that inducers of UGT can decrease circulating thyroid hormones by increasing their biliary excretion. Additionally, the enhanced elimination of thyroid hormones through the phase 2 UGT enzyme system may be the mechanism responsible for increases in serum TSH levels that occur.[28,29] Due to the overlapping of certain antipsychotics and thyroid hormone metabolism, it is possible that competitive inhibition of this enzyme may lead to changes in thyroid hormone levels.[6]

Furthermore, quetiapine is also a piperazine-containing antipsychotic sharing a tricyclic structural nucleus and believed to undergo similar phase 2 biotransformation through glucuronidation. However, it is noted that while it quite likely is glucuronidated like other piperazine-containing antipsychotics, incomplete data are available describing the metabolism of quetiapine.[30] Thus, it is possible that quetiapine, as opposed to risperidone and fluphenazine, which have a different chemical structure, may compete for or inhibit the metabolism of thyroid hormones for phase 2 glucuronidation. This, in turn, may possibly inhibit the metabolism and elimination of T_3 leading to reductions in TSH and T_4 levels. In fact, there is 1 recent report describing 2 cases with 3 to 4 times increases in carbamazepine's active metabolite, carbamazepine-10,11-epoxide, after the addition of quetiapine. The authors suggest that quetiapine may inhibit the glucuronidation of carbamazepine-10,11-trans-diol but also point out that the interaction is possibly due to phase 1 inhibition.[31] Little work has focused on piperazine antipsychotics and their effects on thyroid hormones. Furthermore, to our knowledge, no published work has addressed the relationship of quetiapine to the UGT enzyme system or to its potential link to thyroid hormone changes mediated through this system. We strongly recommend the study of quetiapine through phase 2 metabolism to confirm the postulated mechanisms.

Our study is limited by the small sample size, and these results should be replicated in a larger sample. While it appears that decreases in TT_4 levels are not clinically significant for quetiapine, a larger comparative sample would address the significance and relation of this finding to the other thyroid tests. However, the lack of mean change, small deviations, and few abnormal cases in the risperidone and fluphenazine groups suggest thyroid changes are unlikely with these medications.

This article presents some of the first available data on thyroid function tests with quetiapine in comparison with other antipsychotics in a fixed-dose randomized design. Clinically, the risk for hypothyroidism and the need for monitoring of thyroid function tests during quetiapine treatment have remained questionable. It appears that rou-

tine monitoring is not necessary in patients without a history of thyroid disease on the basis of a literature review and the results of this study. It is also expected that TT_4 levels will decrease during quetiapine treatment, possibly related to competitive metabolism of UGT; however, FT_4I and TSH levels largely remain unaffected. More research is needed on the link between quetiapine, UGT metabolism, and thyroid hormones.

Drug names: benztropine (Cogentin and others), carbamazepine (Carbatrol, Tegretol, and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, Fazaclo, and others), fluphenazine (Prolixin and others), guanfacine (Tenex and others), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), methyldopa (Aldomet and others), olanzapine (Zyprexa), quetiapine (Seroquel), reserpine (Serpalan and others), rifampin (Rifadin, Rimactane, and others), risperidone (Risperdal).

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