A Pilot Study on Risperidone Metabolism: The Role of Cytochromes P450 2D6 and 3A

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Background: The limited available information on plasma risperidone levels shows a stable relationship between daily doses of risperidone and total plasma concentration (risperidone plus its active metabolite 9-hydroxyrisperidone). The ratio between risperidone and 9-hydroxyrisperidone characterizes cytochrome P450 2D6 (CYP2D6) status. According to the manufacturer, the CYP2D6 genotype or drugs that influence CYP2D6 or other cytochrome P450 isoenzyme activity are not expected to be clinically significant. One case report suggests that CYP3A participates in the metabolism of risperidone.

Method: A case series of 13 risperidone patients (the initial case and 12 new cases) who were genotyped for CYP2D6 were followed, and another 20 risperidone patients from a case-control study for the CYP2D6 genotype were reviewed.

Results: The CYP2D6 poor metabolizers, who are enzyme deficient (2/13 in the case series and 3/20 in the case-control study), did not appear to tolerate risperidone well. Drugs affecting CYP3A, in particular powerful inducers and inhibitors, resulted in at least a 2-fold decrease or increase in plasma risperidone levels.

Conclusion: The anecdotal nature of this study is clearly a limitation. Drugs influencing CYP3A and CYP2D6 metabolic activity may significantly affect risperidone levels. Thus, plasma level monitoring of risperidone in a clinical setting may be useful, especially if patients are taking multiple medications or a CYP2D6 deficiency is suspected. New prospective studies under more controlled conditions are needed to verify these hypotheses.

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The atypical antipsychotic risperidone is frequently prescribed in the United States. Cytochrome P450 2D6 deficiency or drugs influencing cytochrome P450 3A activity are not expected to affect risperidone levels in a clinically significant way. We found evidence that either may affect plasma risperidone concentrations.

RISPERIDONE METABOLISM

Risperidone Dose

Several multicenter double-blind studies have indicated that risperidone is an effective antipsychotic agent for the treatment of schizophrenia in dosages ranging from 4–16 mg/day.[1,2] In a U.S. multicenter study,[3] the 6-mg/day dosage was associated with the absence of extrapyramidal (EPS) side effects. This lower risk for EPS has been attributed to risperidone's atypical pharmacodynamic profile of serotonin ($5\text{-}HT_2$) receptor blockade. With doses higher than 6 mg/day, there is a progressive increase in side effects, particularly of the extrapyramidal type. The recommended therapeutic dose of risperidone is lower for geriatric patients,[1] reflecting not only a pharmacokinetic factor (risperidone and its active metabolite are renally excreted), but also a pharmacodynamic factor (decrease of brain dopamine neurons and receptors).

Risperidone Levels

Total active risperidone concentration in plasma reflects the combination of risperidone and its metabolite 9-hydroxyrisperidone. A preliminary study[4] suggested that 9-hydroxyrisperidone is as active as risperidone at the receptor level. Thus, the clinical activity of risperidone is attributable to the actions of the total combined moiety.[5]

Limited information exists correlating plasma risperidone levels with therapeutic outcome and side effects. Existing studies include a sample-dosage design study in 24 schizophrenia patients and a steady-state study in 12 schizophrenia patients.[6,7] The available data on plasma levels from the pharmaceutical company multicenter study show a consistent ratio between the daily dose of risperidone and total plasma concentration of around 7:1.[8] For doses of 2, 6, 10, and 16 mg/day, the respective mean total plasma concentrations were 14, 43, 73, and 111

ng/mL. Due to the linear relationship between dosage and EPS, it is reasonable to project a similar correlation between EPS and plasma risperidone levels. Thus, a total plasma risperidone concentration below 28 ng/mL (corresponding to a 4-mg/day dose) may fall below the therapeutic threshold, and higher concentrations from 42 ng/mL to 112 ng/mL (corresponding to 6 mg/day to 16 mg/day, respectively) would be associated with progressively more risk of EPS.

Risperidone Bioavailability

Risperidone is rapidly and completely absorbed after oral administration, with less than 1% excreted in the feces.[5,9,10] Absolute oral bioavailability of the parent compound in normal metabolizers is 66%, which is mostly attributable to first-pass metabolism (risperidone is converted to 9-hydroxyrisperidone on this first pass). The absolute bioavailability of the active moiety (risperidone plus 9-hydroxyrisperidone) is close to complete (100%) in normal subjects regardless of their metabolic status or route of administration. This stable and complete bioavailability facilitates the use of approximate oral clearance calculations to standardize the surveillance and comparison of total active risperidone moiety concentrations in a patient population on variable daily-dose regimens.

Risperidone Clearance

The ratio of the daily risperidone dose in mg/min divided by serum risperidone moiety concentration at steady state in mg/mL is called oral clearance. According to the data provided by the company, oral clearance varies in a very narrow range from 95 mL/min to 100 mL/min with doses ranging from 2 to 16 mg/day.[8] Utilizing a standard expected normal clearance of 100 mL/min, it is possible to calculate the expected total risperidone moiety concentration for any dose at steady state. Oral clearance is decreased in patients with renal insufficiency (risperidone, 4% to 30% of the administered dose, and 9-hydroxyrisperidone, 8% to 32% of administered dose, can be found in the urine of these patients).[11] Oral clearance can be utilized to identify abnormalities in metabolism and possible drug interactions that alter total risperidone moiety concentration.

Risperidone and Cytochrome P450 2D6

Cytochrome P450 2D6 (CYP2D6) appears to be the main metabolic pathway for many nonpsychiatric drugs (such as β-blockers, antiarrhythmics, and some opioid analgesics), most antipsychotics, and many antidepressants.[12,13] The CYP2D6 enzyme is susceptible to inhibition by some of its substrates, particularly paroxetine and fluoxetine.[13]

CYP2D6 metabolic status is determined by a gene at the long arm of chromosome 22, which shows genetic polymorphism (a stable inherited trait that is not maintained in the population by continuous recurrent mutations). Three major phenotypes have been associated with allelic variation in the CYP2D6 gene: (1) extensive or normal metabolizers, (2) poor metabolizers, and (3) ultrarapid metabolizers. Poor metabolizers have no CYP2D6 enzyme (2 nonfunctioning alleles), and they are referred to as CYP2D6 deficient. They may also develop toxic concentrations of CYP2D6-substrate drugs while taking average doses of those drugs. Extensive (normal) metabolizers are homozygous or heterozygous for the CYP2D6 trait and metabolize CYP2D6 substrates in a normal way. These extensive metabolizers may be converted to phenotypically poor metabolizers by substantial inhibitors such as paroxetine and fluoxetine. Therefore, in clinical situations, 2 types of "phenotypic" poor metabolizers can exist: (1) patients who are genotypically CYP2D6 deficient (enzyme is missing) and (2) patients who are taking drugs that inhibit the CYP2D6 enzyme. Ultrarapid metabolizers with multiple copies of an active CYP2D6 gene have recently been described in 1% to 7% of Caucasian populations in Europe.[14,15] It is believed that ultrarapid metabolizers will have subtherapeutic concentrations of CYP2D6 substrates when administered "average" doses of these substrates.[16] European studies suggest that in the Caucasian population, approximately 90% are extensive (or normal) metabolizers, 7% are poor metabolizers, and 1% to 7% are ultrarapid metabolizers. The proportion of poor metabolizers in those of African and Asian heritage is 1% to 3%.

While poor metabolizers taking risperidone have higher risperidone levels and lower 9-hydroxyrisperidone levels, a preliminary study using CYP2D6 phenotyping in 13 healthy subjects suggests that both poor and extensive CYP2D6 metabolizers have similar total plasma concentrations of the risperidone moiety. As risperidone and 9-hydroxyrisperidone are considered approximate in their pharmacodynamic activity, it has been suggested that the polymorphic CYP2D6 is therapeutically unimportant in patients taking risperidone.[10]

CYP2D6 converts risperidone via aliphatic hydroxylation to the active metabolite 9-hydroxyrisperidone. This 9-hydroxylation is thought to be risperidone's main metabolic pathway, with CYP2D6 the rate-limiting enzyme.[10] Risperidone and 9-hydroxyrisperidone are also degraded via oxidative *N*-dealkylation[5] by an unknown enzyme or enzymes. According to the package insert,[17] drugs that can influence CYP2D6 or other cytochrome P450 isoenzymes are not expected to result in clinically significant interactions.

Ratio of Plasma Risperidone to 9-Hydroxyrisperidone

The ratio between risperidone and 9-hydroxyrisperidone is an indicator of the CYP2D6 isoenzyme metabolic status. Preliminary information suggests that extensive (normal) CYP2D6 metabolizers have a ratio of risperi-

done to 9-hydroxyrisperidone significantly lower than 1.0, usually between 0.1 and 0.3.[18] Calculations using the information from a multicenter study provided by the manufacturer[8] suggest that this ratio is stable and changes minimally with respect to dose (2 mg/day, 0.29; 6 mg/day, 0.27; 10 mg/day, 0.21; 16 mg/day, 0.13). When the CYP2D6 pathway is nonfunctional, serum risperidone (the numerator) predominates, and the ratio is inverted. Poor metabolizers appear to have inverted ratios higher than 1.0.[18]

To summarize, in current clinical practice only advanced age and renal disease are routinely considered reasons to modify risperidone dosages. Moreover, neither the CYP2D6 genotype nor potential drug interactions are routinely considered in risperidone dosing.[19,20] Based on the data presented in the literature, CYP2D6 poor metabolizers should have side effects similar to those of extensive metabolizers, since they have similar total concentrations of active moiety. Drugs influencing CYP2D6 are expected to affect the ratio between risperidone and 9-hydroxyrisperidone, but not the total concentration. Other cytochrome P450 isoenzymes are not thought to be important in risperidone metabolism.

BACKGROUND OF THIS STUDY

Another cytochrome P450 isoenzyme, CYP3A, accounts for 25% of cytochrome P450 present in the human liver and is the most important CYP in the gut.[21] CYP3A metabolizes many psychiatric medications and is also a metabolic pathway for many endogenous esteroids, antihistaminics, calcium channel blockers, and anticholesterol agents. CYP3A is induced by antiepileptics and potent glucocorticoids and inhibited by nefazodone, fluoxetine, fluvoxamine, several antibiotics, and ketoconazole. It is important to know if a drug is metabolized by CYP3A because CYP3A inhibitors and inducers may have extraordinary influence on plasma drug concentrations.[22]

Our initial experience with one patient (case 0) suggested that carbamazepine decreased the total risperidone concentrations (and increased oral clearance) by greater than 2-fold.[23] Moreover, as it is described in Table 1, this had an impact on side effects. The role of carbamazepine as a potent inducer of the CYP3A isoenzyme[18] suggests CYP3A participation in the metabolism of risperidone and indicates a potential for other CYP3A-risperidone interactions.[23]

Consequently, we decided to follow risperidone levels of our inpatients at a state hospital. This study is a report of our observations accumulated over 1 year of following risperidone levels in a case series of 12 new patients and in 20 additional patients receiving risperidone who took part in a case-control study for CYP2D6 genotyping.

METHOD

Case Series

Eastern State Hospital (ESH), Lexington, Ky., is a 160-bed hospital that serves as the primary psychiatric hospital for one third of Kentucky and receives approximately 1600 admissions per year. The most chronic patients are hospitalized for several months or years in a research unit with 30 beds. The senior author (J.d.L.) has been conducting psychopharmacologic research in state hospitals for 10 years and has been the attending psychiatrist of the research unit for the last year. He assessed side effects of antipsychotic medications using the Simpson-Angus Neurologic Rating Scale, the Abnormal Involuntary Movement Scale, and the Barnes Akathisia Scale. The frequency of the assessments and plasma concentration measurements was determined by patient clinical needs. Additional plasma levels were assayed when CYP450 substrates were changed. CYP2D6 genotyping was conducted to help interpret risperidone levels. During this 1-year study period on the research unit, 13 of 35 patients received risperidone. Two elderly patients taking < 1 mg/day of risperidone refused study consent and were not included in the data analysis. The remaining 11 included the patient previously discussed (case 0) and 10 new cases (cases 1–3 and 6–12). Nine of these chronic inpatients at ESH were already taking risperidone for a mean duration of 16 months prior to the beginning of the study. Only 2 patients were started on risperidone treatment by J.d.L. (cases 2 and 12). Patients were closely followed for many months. Two additional cases (4 and 5) who were seen as inpatients in the acute psychiatric unit at the University of Kentucky by J.A.B. were also included in the study. These 2 patients had plasma risperidone concentration measured to evaluate potential drug interactions that may have contributed to their clinical presentation.

Table 1 provides a summary of clinical data. It describes the age, gender, and diagnosis of all 13 patients. All patients were Caucasian except case 12, who was African American. Table 1 also describes side effects in the context of the drug interactions, dose, ratio of risperidone to 9-hydroxyrisperidone, and variations of oral clearance. Variations of clearance 2 times higher or lower than the expected 100 mL/min are noted.

Table 2, the pharmacologic table, describes risperidone genotype and values for risperidone dose, plasma concentrations, oral clearance, and ratio of risperidone to 9-hydroxyrisperidone.

Case-Control Study

A concurrent study of the CYP2D6 genotype was ongoing at ESH during this period. One hundred newly admitted patients were tested for the CYP2D6 genotype.[24] These patients were treated by the attending physicians of

Table 1. Clinical Table: Diagnosis, Risperidone Dose, Drug Interactions, and Side Effects

Case No.	Age (y)	Sex	Diagnosis	Risperidone Dose (mg/d)	Other Drugs	Enzyme Effects of Other Drugs	Ratio[a]	Oral Clearance[b]	Relevant Side Effects
0[c]	22	M	Schizophrenia	4	Carbamazepine	3A4 inducer	Normal	Fast	
				8	Carbamazepine	3A4 inducer	Normal	Fast	
				8	No carbamazepine		Normal	Normal	Severe akathisia
1	39	M	Mental retardation	12	Phenytoin + mesoridazine	3A4 inducer 3A4 inducer	NA	Fast	
				9	Phenytoin only	3A4 inducer	Normal	Normal	Parkinsonian tremor/akathisia
2	54	F	Bipolar disorder	13	Nefazodone	3A inhibitor	Normal	Normal	Severe akathisia and tremor
3[d]	45	F	Schizophrenia	6			Inverted	Slow	Severe TD
				2			Inverted	Slow	Severe TD
4	41	F	Major depression	4	Fluoxetine	2D6 and 3A inhibitor	Inverted	Slow	Drowsiness and poor concentration
5	18	M	Major depression	4	Fluoxetine + buspirone	2D6 and 3A inhibitor 3A competitor	Inverted	Slow	Sedation and poor academics
6	44	F	Bipolar disorder	6	Paroxetine + mesoridazine	2D6 inhibitor 3A4 inducer	Normal	Normal	
				6	Paroxetine only	2D6 inhibitor	Inverted	Normal	
7	42	M	Schizoaffective disorder	6	Paroxetine + mesoridazine	2D6 inhibitor 3A4 inducer	NA	Fast	
				8	Paroxetine + mesoridazine	2D6 inhibitor 3A4 inducer	Normal	Normal	
				8	Paroxetine only	2D6 inhibitor	Inverted	Normal	
8[d]	37	M	Schizophrenia	12	Mesoridazine + buspirone	3A inducer 3A competitor	Inverted	Normal	Parkinsonian tremor
				12	Mesoridazine	3A inducer	Inverted	Fast	Corrected by anticholinergics
				12	Olanzapine	Not well known	Inverted	Normal	
9	27	M	Psychiatric disorder due to medical condition	6	Paroxetine	2D6 inhibitor	Normal	Normal	
				6	No paroxetine		Normal	Normal	
10	55	M	Schizoaffective disorder	15			Normal	Normal	Parkinsonian tremor
11	47	F	Bipolar disorder	16			Normal	Normal	
				16	Olanzapine	Not well known	Normal	Normal	
12	42	M	Mental retardation	2	Haloperidol decanoate	2D6 and 3A competitor	Normal	Normal	

[a]Ratio: risperidone/9-hydroxyrisperidone concentration in plasma; normal, < 1; inverted, > 1; and NA, not applicable.
[b]Oral clearance of risperidone, fast: > 200 mL/min, slow: < 50 mL/min.
[c]Our initial contact with case 0 prompted our investigation into cases 1–12.
[d]Cytochrome P450 2D6 (CYP2D6) deficient.

the acute care unit. During the first 3 days of admission, patients were assessed for side effects by a rater who was blind to CYP2D6 genotype. Twenty of these patients were taking risperidone when admitted.

CYP2D6 Genotype

The CYP2D6 genotyping was conducted at the University of Kentucky College of Pharmacy (P.J.W.). Blood samples for CYP2D6 genotyping were analyzed using polymerase chain reaction (PCR), which detects A, B, D, E, T, and Lxn alleles (*3, *4, *5, *7, *6, and *2xn). Negative quality controls have detected no contamination problems with the PCR, and positive quality controls indicate that the results are reproducible.[25] The A, B, D (deletion), E, and T (*3, *4, *5, *7, *6) alleles have been reported in poor metabolizers. Any combination of these alleles (e.g., A/A, T/T, A/B, A/D, E/T) is associated with poor metabolism. Extensive metabolizers are homozygous or heterozygous for the dominant wild type alleles. Table 2 describes patient alleles. There were 2 poor metabolizers (case 8 and case 3) in the case series.

In the 20 risperidone patients of the case-control study, there were 3 CYP2D6 poor metabolizers (cases) and 17 extensive metabolizers (controls).

Risperidone Levels

Risperidone and 9-hydroxyrisperidone levels were measured using the hospital's routine commercial laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, Calif.). The analytic method used was high-performance liquid chromatography (HPLC).[26] The coefficient of variance for low concentrations (8–12 ng/mL) is 10% for 9-hydroxyrisperidone and 9% for risperidone. For higher concentrations, it is 11% for 9-hydroxyrisperidone

Table 2. Pharmacologic Table: CYP2D6 Genotype, Plasma Risperidone Concentration, Oral Clearance, and Ratio[a]

Case No.	CYP2D6 Genotype	Risperidone Dose (mg/d)	R (ng/mL)	9-OH-R (ng/mL)	Total Moiety (ng/mL)[b]	Oral Clearance (mL/min)	Ratio[c]	Other Drugs
0[d]	wt/wt	4	< 5	10	10	278	< 0.5	Carbamazepine
		8	< 5	19	19	292	< 0.3	Carbamazepine
		8	< 5	49	49	113	< 0.1	No carbamazepine
1	wt/wt	12	< 5	< 10	< 15	> 555	NA	Phenytoin + mesoridazine
		9	< 5	32	32	195	< 0.2	Phenytoin only
2	wt/wt	13	11	130	141	64	0.08	Nefazodone
3	B/B[e]	6	79	17	96	43	4.3	
		2	27	8	36	39	3.4	
4	wt/wt	4	66	29	95	29	2.3	Fluoxetine
5	wt/?	4	108	10	118	24	9.2	Fluoxetine + buspirone
6	wt/B	6	9	14	23	181	0.7	Paroxetine + mesoridazine
		6	41	37	78	53	1.3	Paroxetine only
7	wt/B	6	< 5	< 10	< 15	> 277	NA	Paroxetine + mesoridazine
		8	12	17	29	191	0.7	Paroxetine + mesoridazine
		8	57	41	98	57	1.4	Paroxetine only
8	D/D[e]	12	84	20	104	80	4.2	Mesoridazine + buspirone
		12	30	10	40	208	3.0	Mesoridazine only
		12	59	17	76	109	3.4	Olanzapine
9	wt/wt	6	32	42	74	56	0.8	Paroxetine
		6	< 5	44	44	95	< 0.1	No paroxetine
10	wt/wt	15	5	59	64	162	0.1	
11	wt/B	16	< 5	58	58	192	< 0.1	
		16	< 5	64	64	174	< 0.1	Olanzapine
12	wt/wt	2	< 5	19	19	73	< 0.3	Haloperidol decanoate

[a]Abbreviations: 9-OH-R = plasma 9-hydroxyrisperidone concentration, R = plasma risperidone concentration, wt = dominant wild type allele, NA = not applicable.
[b]Total moiety: risperidone + 9-hydroxyrisperidone plasma concentrations.
[c]Ratio: risperidone/9-hydroxyrisperidone concentration in plasma.
[d]Our initial contact with case 0 prompted our investigation into cases 1–12.
[e]CYP2D6 deficient.

and 7% for risperidone. The quantitative plasma concentration threshold is 10 ng/mL for 9-hydroxyrisperidone and 5 ng/mL for risperidone. The half-life of the parent compound risperidone in an extensive (normal) metabolizer is approximately 3 hours. Standard morning risperidone trough concentrations for twice-a-day dosing in some patients were below the 5-ng/mL threshold, particularly for doses lower than 6 mg/day.

RESULTS

Since the patients in the case series were taking other medications that affect different metabolic pathways, the results will be presented according to the proposed effect of concomitant medications or metabolic status on risperidone metabolism. Since plasma concentrations were not measured in the case-control study, the data only include the relationship of side effects with CYP2D6 deficiency.

Effect of CYP3A Inducers

Carbamazepine, mesoridazine, and phenytoin[18] are CYP3A inducers. Case 0 was the first that suggested the induction of the CYP3A may significantly decrease risperidone levels (and increase oral clearance). Table 1 illustrates that the discontinuation of carbamazepine without changing risperidone dose (8 mg/day) was associated with severe akathisia. Risperidone was discontinued, and the patient was eventually stabilized on olanzapine.

Case 1 was taking a high dose of risperidone (12 mg/day), but levels were repeatedly undetectable, suggesting an oral clearance at least 5 times the expected rate. One of 2 CYP3A inducers, mesoridazine, was discontinued and risperidone levels rose to detectable levels, although still only half its expected concentration (which may be due to the effect of phenytoin, the other CYP3A inducer). The patient developed akathisia and parkinsonian tremor that improved when risperidone was progressively decreased.

Effect of CYP3A Inhibition

While taking nefazodone, a substantial CYP3A inhibitor, case 2 had a very high total moiety of risperidone (141 ng/mL) associated with severe akathisia and parkinsonism. The high levels may be explained by a high dose (13 mg/day) and by the effect of nefazodone, which competitively inhibits CYP3A and appears to decrease oral clearance by almost half. Risperidone was discontinued.

Effect of Being a Poor Metabolizer of CYP2D6

Of the 13 patients in the case series, 2 were determined to be CYP2D6 deficient (cases 3 and 8). In the case-

control study, there were 3 patients who were CYP2D6 deficient.

Case 3, a woman with schizophrenia, exhibited a severe case of tardive dyskinesia while taking risperidone (6 mg/day). The unexpectedly high levels of risperidone (79 ng/mL) and inverted risperidone/9-hydroxyrisperidone ratio of 4.3 suggested that she was unable to metabolize risperidone via CYP2D6. The patient was taking no other medications, and she had a history of intolerance to typical antipsychotics. We suspected that she was genetically CYP2D6 deficient, which was verified by the genotype. A reduction of the dose to 2 mg/day was associated with a parallel reduction in plasma concentrations. Eventually, risperidone was discontinued, and her psychotic symptoms and dyskinetic movements improved significantly with a low dose of olanzapine.

Review of the case-control study also suggested that subjects lacking CYP2D6 may be very prone to side effects while on risperidone therapy. Of the 20 patients taking risperidone at admission (daily mean ± SD dose = 5 ± 2.4; range, 2–10 mg/day), 3 (15%) were poor metabolizers and 17 (85%) were extensive metabolizers. The prevalence of at least moderate side effects from risperidone was 100% (3/3) in the poor metabolizers and 35% (6/17) in the extensive metabolizers (Fisher exact test, 2-tail, $p = .074$). Patients were taking different risperidone doses and drug combinations. Therefore, it is striking that the difference in side effects in poor versus extensive metabolizers is strong enough to almost reach significance in this very small sample.

Effect of Inhibiting Both CYP3A and CYP2D6

At the usually minimum recommended dose, fluoxetine treatment produces substantial inhibition of CYP2D6 and CYP3A, which is a concentration-dependent phenomenon.[27] Two nonpsychotic community patients who were taking risperidone in combination with fluoxetine were acutely hospitalized with multiple psychiatric and physical complaints.

Case 4, a woman with depression, complained of difficulty concentrating, dissociative type symptoms, drowsiness, and restlessness that affected her job performance and daily commute to work. The risperidone dose was relatively low (4 mg/day), but it was combined with 40 mg/day of fluoxetine. Her total risperidone moiety was unexpectedly high (95 ng/mL), her oral clearance was slow (a third of the expected rate) in conjunction with a large inverted ratio. She was discharged with some symptom improvement after dose modification. Her genotype showed that she was an extensive metabolizer.

Case 5, a young male extensive metabolizer, was admitted because of depressive complaints, sedation, poor academic performance (poor concentration and memory), intermittent periods of restlessness, and recent gastrointestinal complaints including nausea and vomiting. He was taking a low dose of risperidone (4 mg/day) with 40 mg/day of fluoxetine. Risperidone oral clearance was the lowest of any patient studied, the risperidone/9-hydroxyrisperidone ratio was impressively large (9.2), and the total active risperidone moiety (118 ng/mL) was more than 4 times the expected. The patient was also taking buspirone, which appears to be metabolized by CYP3A (data on file, Bristol-Myers Squibb, Princeton, N.J., 1996). His symptoms resolved when risperidone was discontinued, and his other medications were not given. He was discharged taking 20 mg/day of fluoxetine only.

Effect of Decreased CYP2D6 Activity and Induction of CYP3A

At a usual therapeutic dose, paroxetine is a substantial inhibitor of CYP2D6.[27] Mesoridazine appears to be a CYP3A inducer. Two extensive metabolizers, cases 6 and 7, were taking this combination of medications. The ratio was 0.7 for both patients. Although one might expect an inverted ratio from the inhibitory effects of paroxetine, it appears that the inductive properties of mesoridazine partially override the effects of paroxetine.

Further evidence of the effects of CYP3A induction and decreased CYP2D6 activity on risperidone metabolism can be seen in case 8, a poor metabolizer. He was taking mesoridazine and buspirone, a CYP3A substrate. When buspirone was discontinued, the oral clearance of risperidone increased more than 2-fold, which may be attributed to induction by mesoridazine. However, due to the underlying CYP2D6 deficiency, the risperidone/9-hydroxyrisperidone ratio remained inverted throughout therapy. The patient had poor tolerance of risperidone and needed high doses of anticholinergics to control tremor and akathisia. He did not subsequently exhibit these side effects while taking olanzapine or clozapine, 2 antipsychotics whose primary metabolic pathway is not via CYP2D6.

Inhibition of CYP2D6

As noted above, paroxetine is a substantial inhibitor of CYP2D6. Patient 9 was taking paroxetine (40 mg/day) and exhibited some minor changes in his risperidone/9-hydroxyrisperidone ratio (0.8) and in oral clearance of the total moiety, which reverted to more typical values after discontinuation of paroxetine. Patients 6 and 7 (described in prior section) displayed inverted risperidone moiety ratios (1.3 and 1.4) without major changes in the oral clearance when taking only paroxetine, 20 mg/day (see Table 1).

Other Patients

There were 4 patients (cases 9, 10, 11, and 12) who displayed no major variations of oral clearance or risperidone/9-hydroxyrisperidone ratio. One patient was taking a low dose of haloperidol decanoate, which was not associated with any major impact on risperidone clearance.

The addition of olanzapine (patients 11 and 8) also did not appear to modify risperidone levels.

DISCUSSION

This study is limited because it is not a well-designed scientific study, but rather a collection of anecdotes. However, these data have enhanced our awareness that plasma risperidone concentration monitoring may be helpful in the management of treatment-refractory patients and those taking multiple medications. Examining our data, some consistent trends have emerged that became clearer after reviewing our current knowledge of the cytochrome P450 enzymes and verifying patient CYP2D6 genotype. These trends may have important clinical implications. Acknowledging the limitations of our data, such as the study design, lack of plasma concentrations of other medications, and small sample size, there are still pertinent recommendations for clinicians. Drugs influencing CYP3A may significantly affect risperidone levels. Monitoring plasma risperidone concentrations and side effects when CYP3A inducers or inhibitors are added to risperidone treatment is advised. Fluoxetine may be unique, as it is also a CYP2D6 inhibitor.

The suggestion from the risperidone package insert to disregard the genetic CYP2D6 deficiency may not be prudent. CYP2D6-deficient patients do not appear to tolerate risperidone well. Two poor metabolizers treated by us required a change to other atypical antipsychotics. The review of the other 3 poor metabolizers (from the case-control study) suggests this same pattern. In 2 of these 3 cases, risperidone was discontinued by the treating physician or the patient. This was done without knowledge of the patient CYP2D6 genotype.

Clinicians may identify poor CYP2D6 metabolizers by recognizing prior history of intolerance to typical antipsychotics and/or by checking plasma risperidone concentrations. CYP2D6-deficient subjects appear to have a history of intolerance to most typical antipsychotics. It is not well known to what extent the CYP2D6 enzyme takes part in the metabolism of typical antipsychotics, but it does appear that CYP2D6 has a major role in metabolizing thioridazine, perphenazine, chlorpromazine, and fluphenazine. Clinicians can identify CYP2D6 deficiency in patients taking risperidone at steady state by finding inverted ratios (risperidone levels higher than 9-hydroxyrisperidone) in the absence of CYP2D6 inhibition. However, clinicians need to be aware that an extra bolus of medication shortly before a scheduled blood draw may be manifested as an inverted ratio. Consequently, collecting risperidone levels prior to medication administration in the early morning is recommended. The appropriate management of patients deficient in CYP2D6 may include low-dose risperidone treatment. Other atypical antipsychotics, not significantly dependent on CYP2D6 for their metabolism,[17] may provide alternative treatments. We have successfully used olanzapine and clozapine (quetiapine may be a good choice, but we have not yet tried it with CYP2D6-deficient subjects).

The most important conclusion of this study is that plasma-level monitoring of risperidone in a clinical setting may be useful, especially if patients are taking multiple medications or a CYP2D6 deficiency is suspected.

New prospective studies under more controlled conditions are needed to verify the clinical relationship between risperidone metabolism and the CYP3A and CYP2D6 isoenzymes. We hope that this pilot study will raise some questions and encourage other clinicians and researchers to carry out new studies under more controlled conditions.

Drug names: buspirone (BuSpar), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluoxetine (Prozac), fluphenazine (Prolixin and others), fluvoxamine (Luvox), haloperidol (Haldol and others), ketoconazole (Nizoral), mesoridazine (Serentil), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), perphenazine (Trilafon and others), phenytoin (Dilantin and others), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others).

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