Risperidone in Acutely Exacerbated Schizophrenia: Dosing Strategies and Plasma Levels

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Background: The optimal risperidone dosing strategy for acute schizophrenia requires elucidation. Furthermore, plasma levels of risperidone and its active metabolite (9-hydroxyrisperidone) at a given dose vary greatly among different individuals. For patients who metabolize risperidone slowly, a medium dose results in excessively high plasma levels, which might be related to adverse events and perhaps poor response. We thus investigated whether dose reduction to diminish adverse reactions associated with ordinary risperidone doses could still yield efficacy for acutely exacerbated schizophrenia.

Method: Thirty-one newly hospitalized Chinese patients with acute exacerbation of schizophrenia (DSM-IV) entered this prospective, 6-week open trial. Risperidone doses were titrated to 6 mg/day (if tolerable) over 3 days, but were lowered thereafter if side effects appeared. Efficacy and side effect assessments were conducted on days 0, 4, 14, 28, and 42. Endpoint steady-state plasma levels of risperidone and 9-hydroxyrisperidone were analyzed by high performance liquid chromatography with ultraviolet detection.

Results: Thirty patients completed the trial. Of them, 17 tolerated the 6-mg target dose well, while the other 13 received lower final doses (mean ± SD = 3.6 ± 0.9 mg, $p = .0001$) for curtailing treatment-emergent side effects. At endpoint, 92.3% of the 13 low-dose individuals responded to treatment (20% or more reduction in the total Positive and Negative Syndrome Scale score), compared with 52.9% of the 17 high-dose subjects ($p < .05$). No significant between-group differences were revealed in other minor efficacy measures. Of note, endpoint plasma levels of the active moiety (risperidone plus 9-hydroxyrisperidone) were similar between the low- and high-dose groups (40.4 ± 31.1 ng/mL vs. 49.7 ± 13.4 ng/mL, NS).

Conclusion: The results of this preliminary trial suggest that up to 6 mg of risperidone is efficacious in treating patients with acute exacerbation of schizophrenia. Nearly 60% of the patients could tolerate a 6-mg dose. For the other 40%, reducing dosages to 3.6 ± 0.9 mg for relieving side effects still yielded efficacy. The 2 dose groups were comparable in the endpoint steady-state plasma drug concentrations.

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Risperidone appears effective against both the positive and negative symptoms of schizophrenia.[1–3] The North American multicenter trials[1,2] concerning chronic patients identify a dosage of 6 mg/day (on average) to produce optimal efficacy with the least side effects. Recently, risperidone treatment for general patients has involved efforts to use doses of 4 to 6 mg/day or lower.[4–7] In accordance with this trend, it has been suggested that unduly high doses may be detrimental to risperidone's efficacy.[6,7] Nevertheless, for individuals with acutely exacerbated schizophrenia, mean endpoint doses (8 mg/day,[8] 8.5 mg/day,[9] 8.6 mg/day,[10] 9.7 mg/day,[11] and 12 mg/day[12]) were still rather high in most recent studies but one (enrolling both 4-mg/day and 8-mg/day groups).[13]

Since the interindividual variability of plasma concentrations of risperidone and its active metabolite (9-hydroxyrisperidone)[14] at a given dose is greater than 40-fold,[15–18] the plasma level may more directly determine the clinical effects than the dose itself.[15,16] However, the therapeutic blood levels for risperidone treatment remained to be clarified.[15,19,20] We hypothesized that excessively high levels (even under a medium dose) might be associated with side effects and poor clinical response. Therefore, reducing doses to abate adverse events could decrease the blood drug levels to the therapeutic range (if actually existing), perhaps thus yielding better clinical efficacy. The main aim of this study was to preliminarily test this a priori hypothesis in schizophrenic inpatients with acute exacerbation. Risperidone doses were titrated to 6 mg/day (if tolerable) over 3 days, but were reduced thereafter if side effects appeared. We assumed that the patients tolerating the 6-mg target dose well were compa-

rable with those receiving lower dosages in terms of endpoint (week 6) plasma drug concentrations, drug efficacy, and side effects. In addition, our secondary aim was to analyze the relationships between clinical response and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone.

METHOD

This was a prospective, open-label study conducted in an acute psychiatric ward in Taipei City Psychiatric Center, Taipei, Taiwan. The protocol was approved by the facility's institutional review board.

Subjects

All newly hospitalized patients with acute exacerbation of schizophrenia were screened and evaluated by experienced psychiatrists. Patients entered this study if they (1) were physically healthy and had all laboratory parameters within normal limits, (2) were aged 18 to 60 years, (3) satisfied DSM-IV criteria for schizophrenia, (4) had a minimum baseline total score of 60 on the Positive and Negative Syndrome Scale (PANSS),[21] (5) had no DSM-IV diagnosis of substance (including alcohol) abuse, (6) were nonsmokers, (7) had not received depot antipsychotics for the preceding 6 months, (8) had no history suggesting that neuroleptic treatment would be contraindicated, and (9) gave written informed consent and were competent to do so.

Study Design

The study was then divided to 2 stages:

Stage 1 (washout period). The subjects were placed on placebo treatment for 7 days, which could be shortened to a minimum of 1 day for patients with extremely emergent psychotic symptoms. The required washout period in this study involving newly admitted patients with acute symptoms was thus shorter than that (at least 3 days) in most previous investigations. It has been recently suggested that medication-free periods may be unnecessary for clinical drug trials and even detrimental to the patients.[22]

Stage 2 (active treatment period). The patients were given 1 mg of risperidone b.i.d. on day 1, then 2 mg b.i.d. on day 2, and 3 mg b.i.d. on day 3. In case of dose intolerance, the escalation rate was slowed down during this 3-day titration period. From day 4 to day 42, the dosage either remained the same as that used on day 3 or could be reduced on day 4, day 14, or day 28 after the drug safety evaluation (see Clinical Assessment below). Patients were defined a priori as responders if they had a reduction of 20% or more in the PANSS total score from baseline. Both the subjects participating for at least 42 days and those terminating (for discharge from hospital) on day 28 because response criteria were met were defined as completers. At endpoint (day 42, or day 28 for the fast responders), those receiving the target dose of 6 mg were compared with the other patients who did not attain that dose in terms of background characteristics, drug efficacy, side effects, and plasma drug levels.

Lorazepam was allowed as needed for insomnia (p.o.) or agitation (i.m.), and benztropine was allowed for extrapyramidal side effects (EPS). No other centrally acting drugs or cytochrome P450 inducers (or inhibitors) that might interfere with risperidone's metabolism[14,17,23,24] were permitted.

Clinical Assessment

The raters, patients, and clinical staff all were unaware of our dosing hypothesis and the laboratory results. Efficacy and side effect assessments were conducted on days 0, 4, 14, 28, and 42. The main efficacy instrument was the PANSS. Other measures included the Clinical Global Impressions (CGI) scale,[25] the Nurses' Observation Scale for Inpatient Evaluation (NOSIE),[26] and the Global Assessment of Functioning (GAF; DSM-IV Axis V). The raters for the PANSS were trained using videotapes of standardized PANSS interviews. Their performance was then tested by assessing 3 additional patient interviews. Each rater was required to achieve an intraclass correlation coefficient (ICC) of at least 0.80 to participate in the trial. Raters were retested at the end of the trial, and no rater's ICC fell below 0.80.

Drug safety was evaluated by means of routine physical and neurologic examinations, laboratory tests, determination of body weight, the Extrapyramidal Symptom Rating Scale (ESRS),[27] and the UKU Side Effect Rating Scale.[28] The ESRS was designed to evaluate 3 types of EPS: parkinsonism, dystonia, and dyskinesia.[27] Other side effect profiles were determined by the UKU scale.

Laboratory Assessment

Steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone were measured at endpoint. Blood samples were taken 11 to 12 hours after the evening dose and prior to the morning dose. Venous blood was collected into an EDTA tube and centrifuged at 3000 rpm for 15 minutes. Plasma samples were stored at –60°C until assayed. The determinations of risperidone and 9-hydroxyrisperidone were performed by high performance liquid chromatography (HPLC) using ultraviolet detection. An LC-18 PK/108 solid-phase cartridge (Supelco, Bellefonte, Pa.) with a vacuum manifold was used for plasma extraction. Prior to the application of the sample, the clean-up cartridge was conditioned by consecutive rinses with 1 mL of methanol and 1 mL of water. One milliliter of plasma sample was mixed with 50 μL (3.2 μg/mL) of methylrisperidone (the internal standard) and 1 mL of 0.2 M potassium chloride (which was adjusted to pH 12.0 using 0.2 M sodium hydroxide) and then

applied into the cartridge. After being washed with 50% methanol in water (vol/vol), the analytes were eluted with 1 mL of 0.01 M acetic acid in methanol. The final eluate was evaporated to dryness and then dissolved in 200 μL of HPLC eluent for subsequent HPLC analysis.

The HPLC set was equipped with a Waters 600-MS system controller, a Waters 717 WISP autosampler, and a Spectra Series UV 150 ultraviolet detector. Separations were performed on a reverse-phase Waters Nova-Pak phenyl column (3.9 × 150 mm; 4 μm particle size; Waters, Milford, Mass.). The mobile phase was composed of 0.05 M of potassium phosphate and acetonitrile (70:30, vol/vol, pH = 6.5 with 1 M KOH). All water was Milli-Q grade. The isocratic separation was performed at 0.9 mL/min flow-rate at ambient temperature. The eluent was monitored by the ultraviolet detector at a wavelength of 277 nm. As a result, the retention times of 9-hydroxyrisperidone, risperidone, and methylrisperidone were 4.3, 7.2, and 12.0 min, respectively. The curves of risperidone and 9-hydroxyrisperidone were linear over a range of 2 to 150 ng/mL. The signal-to-noise ratio at the lower limit of quantitation, 2 ng/mL, was 3 or more for each analyte. The curve for the parent compound was defined by the equation $y = 0.0191x - 0.0174$ (coefficient of correlation = 0.999, N = 6) and for the metabolite by $y = 0.0256x - 0.0102$ (coefficient of correlation = 0.999, N = 6). For each compound, both within-day and between-days coefficients of variance were less than 15% in the range of 2 to 150 ng/mL. The concomitant drugs (lorazepam and benztropine) permitted in this trial showed no interference with risperidone, 9-hydroxyrisperidone, or the internal standard. The extraction recoveries of risperidone and 9-hydroxyrisperidone were consistent throughout the curve concentration range of the analytes. The mean ± SD overall recovery was 86.8% ± 5.2% for risperidone and 74.0% ± 5.1% for 9-hydroxyrisperidone. Recovery of the internal standard was 82.7% ± 3.7%.

Statistical Methods

For between-group comparisons, 2-sided Student t tests were used for dimensional data, while 2-tailed chi-square tests or Fisher exact tests were used for categorical data. Linear and quadratic models for response versus plasma drug levels were performed by regression analysis. Quadratic regression analysis was used to test for the presence of a curvilinear response function. Statistical significance was defined as $p < .05$.

RESULTS

Thirty-one inpatients entered this study. One subject dropped out on day 10 owing to withdrawal of consent, 26 finished the 42-day trial, and the other 4 showed early response (≥ 20% improvement in a PANSS total score) and terminated (because of discharge upon their request) on day 28. According to our design, the latter 30 (13 women/17 men, mean ± SD age = 36.1 ± 9.6 years, mean ± SD body weight = 59.0 ± 11.4 kg) were considered completers.

Table 1. Characteristics of Schizophrenic Patients Treated With Low (< 6 mg/day) or High (6 mg/day) Doses of Risperidone

	Low-Dose Group (N = 13)		High-Dose Group (N = 17)		
Characteristic	Mean	SD	Mean	SD	p Value[a]
Age, y	37.0	8.2	35.4	10.7	NS
Body weight, kg	56.0	11.7	59.8	10.0	NS
Duration of education, y	11.8	2.8	10.9	4.7	NS
Age at onset of psychosis, y	26.8	9.5	24.1	8.9	NS
Age at first hospitalization, y	33.0	8.5	28.1	10.6	NS
Number of hospitalizations	0 .9	1.6	2.7	3.0	< .05

[a]2-sided Student t test.

The mean ± SD final dose for these 30 patients was 5.0 ± 1.3 mg/day. Of these patients, 17 tolerated the target dose of 6 mg/day well. However, the other 13 experienced intolerable side effects: sinus tachycardia (N = 4), akathisia (N = 3), orthostatic dizziness (N = 2), sedation (N = 2), insomnia (N = 1), and tremor (N = 1). For curtailing such adverse events, these 13 thus received significantly lower final doses (3.6 ± 0.9 mg; range, 2–5 mg; p = .0001) than their 17 high-dose counterparts. At earlier timepoints, the mean daily doses used in the 13 low-dose patients were 5.2 ± 1.5 mg on day 4 (before clinical assessment; not significant [NS] compared with the high-dose group), 4.5 ± 1.9 mg on day 14 ($p < .05$), and 3.9 ± 1.4 mg on day 28 ($p < .0005$). Interestingly, the low-dose patients showed equal or perhaps even superior response to the high-dose individuals (as described in Drug Efficacy and Plasma Levels below). Three subjects in the low-dose group and 4 in the high-dose group received lorazepam injections i.m. for agitation during the trial. At endpoint, the mean p.o. dose of lorazepam (1.6 ± 1.4 mg/day vs. 1.3 ± 1.3 mg/day) or benztropine (1.2 ± 1.5 mg/day vs. 0.8 ± 1.2 mg/day) and the percentage of patients using lorazepam (69.2% vs. 88.2% [9/13 vs. 15/17]) or benztropine (53.8% vs. 52.9% [7/13 vs. 9/17]) did not differ significantly between the low-dose and high-dose groups.

The low-dose group consisted of 6 men and 7 women; the distribution of schizophrenia subtypes in the group was 8 paranoid, 2 disorganized, and 3 undifferentiated. The high-dose group consisted of 11 men and 6 women; the schizophrenia subtypes were 10 paranoid, 4 disorganized, and 3 undifferentiated. Demographic features of the 30 subjects are listed in Table 1. No significant differences were found between the 2 dose groups with respect to most demographic variables and baseline scores of the PANSS total and 3 PANSS subscales (Table 2). However, the number of prior hospitalizations was significantly

Table 2. Change in Positive and Negative Syndrome Scale (PANSS) Scores of Schizophrenic Patients Treated With Low (< 6 mg/day) or High (6 mg/day) Doses of Risperidone

	Low-Dose Group (N = 13)		High-Dose Group (N = 17)		
Assessment	Mean	SD	Mean	SD	p Value[a]
Positive PANSS					
Baseline score	21.3	3.8	22.3	5.2	NS
Endpoint score	13.6	4.7	15.1	4.5	NS
% Change at endpoint	–36.1	16.2	–30.6	16.5	NS
Negative PANSS					
Baseline score	26.0	5.7	28.2	6.4	NS
Endpoint score	19.0	7.0	23.1	7.4	NS
% Change at endpoint	–27.4	16.8	–18.7	13.3	NS
General PANSS					
Baseline score	39.2	5.7	38.9	10.5	NS
Endpoint score	27.2	7.1	28.9	7.4	NS
% Change at endpoint	–30.4	15.3	–22.3	19.3	NS
Total PANSS					
Baseline score	86.5	11.6	89.4	18.6	NS
Endpoint score	59.8	16.6	67.1	17.8	NS
% Change at endpoint	–31.2	13.7	–23.7	15.6	NS
	N	%	N	%	
Responders (≥ 20% improvement in total PANSS score)	12/13	92.3	9/17	52.9	< .05

[a]2-tailed Fisher exact test for responders; 2-sided Student t test for other variables.

fewer in the low-dose group than in the high-dose group (see Table 1).

Drug Efficacy and Plasma Levels

For all 30 subjects, the mean ± SD percentage reduction from baseline to endpoint was 26.9% ± 15.0% in the PANSS total, 33.0% ± 16.3% in the PANSS positive subscale, 22.5% ± 15.3% in the negative subscale, and 25.8% ± 17.9% in the general psychopathology. Twenty-one (70%) of the 30 met response criteria.

In the between-group comparison, the low-dose group tended to excel, albeit statistically insignificantly, in percentage change in the PANSS total and 3 PANSS subscale scores (see Table 2). Nevertheless, a significantly higher percentage of low-dose patients than high-dose individuals responded to treatment at endpoint (92.3% vs. 52.9%, $p < .05$) (see Table 2). At earlier times, the responder rates in the 2 groups were not significantly different: 15.4% vs. 11.8% (2/13 vs. 2/17) on day 4, 46.2% vs. 41.2% (6/13 vs. 7/17) on day 14, and 69.2% vs. 52.9% (9/13 vs. 9/17) on day 28.

With regard to the minor efficacy measurements (CGI, NOISE, and GAF), no significant between-group differences were found in either baseline or endpoint scores. At baseline, mean ± SD CGI severity scores were 4.4 ± 0.7 and 4.4 ± 1.0 in the low-dose and high-dose groups, respectively, and at endpoint, 3.3 ± 0.6 and 3.5 ± 1.1, respectively. As for the NOSIE, the mean baseline scores were 73.3 ± 15.8 and 76.6 ± 18.6 for the 2 groups, respectively, and the endpoint scores were 58.2 ± 14.3 and 61.4 ± 17.2. Finally, for the GAF, the mean baseline scores were 41.4 ± 6.6 and 41.5 ± 8.5, respectively, and the endpoint scores, 55.3 ± 9.2 and 53.7 ± 10.1.

Of note, in the low- and high-dose groups, steady-state plasma risperidone (7.8 ± 11.8 ng/mL vs. 7.3 ± 7.6 ng/mL), 9-hydroxyrisperidone (32.6 ± 21.1 ng/mL vs. 42.4 ± 7.7 ng/mL), risperidone plus 9-hydroxyrisperidone (40.4 ± 31.1 ng/mL vs. 49.7 ± 13.4 ng/mL), and risperidone to 9-hydroxyrisperidone ratios (0.19 ± 0.18 vs. 0.16 ± 0.16) were similar at endpoint (each NS). No significant linear or quadratic relationships were found between each plasma parameter (risperidone, 9-hydroxyrisperidone, the sum of both, or the ratio of risperidone to 9-hydroxyrisperidone) and score changes or percentage changes in the PANSS total or 3 subscales. For all 30 subjects, administration of each mg of risperidone could produce steady-state plasma risperidone levels of 1.5 ± 2.1 ng/mL; 9-hydroxyrisperidone, 8.0 ± 3.6 ng/mL; the sum, 9.5 ± 5.2 ng/mL; and the ratio, 0.18 ± 0.17.

Side Effects and Plasma Levels

The 13 patients experiencing side effects initially, after dose reduction, were much relieved of those side effects at endpoint. Thus, the residual adverse events in these low-dose individuals were minimal (if any) at the end and comparable with those in the high-dose group, who tolerated the target dose well.

The mean endpoint (baseline) ESRS scores of the low-dose and high-dose groups were similar: parkinsonism score = 0.5 ± 0.7 (1.2 ± 2.6) vs. 1.2 ± 2.3 (0.9 ± 2.5), dystonia score = 0.5 ± 1.7 (0.2 ± 0.6) vs. 0.0 ± 0.0 (0.0 ± 0.0), dyskinesia score = 0.4 ± 1.4 (1.5 ± 4.5) vs. 0.1 ± 0.2 (0.0 ± 0.0), and total ESRS score = 1.5 ± 3.0 (2.8 ± 6.0) vs. 1.2 ± 2.3 (0.9 ± 2.5). Furthermore, many patients were free of EPS at endpoint. The percentages of patients who scored 0 on each ESRS measure were similar between the 2 groups: parkinsonism score, 53.6% vs. 64.7% (7/13 vs. 11/17); dystonia score, 84.6% vs. 100.0% (11/13 vs. 17/17); dyskinesia score, 92.3% vs. 94.1% (12/13 vs. 16/17); and total score, 46.1% vs. 58.8% (6/13 vs. 10/17).

Regarding the UKU scale, the following 6 adverse events were experienced by 10% or more of the low- or high-dose patients at endpoint: weight gain, 23.1% (3/13) of the low-dose patients vs. 29.4% (5/17) of the high-dose patients; akathisia, 23.1% vs. 5.9% (3/13 vs. 1/17); tremor, 7.7% vs. 17.7% (1/13 vs. 3/17); dystonia, 15.4% vs. 5.9% (2/13 vs. 1/17); sedation, 15.4% vs. 0.0% (2/13 vs. 0/17); and rigidity, 0.0% vs. 11.8% (0/13 vs. 2/17). No significant differences were found between the 2 groups for these 6 events. At baseline, no between-group differences were observed for these items, either.

Plasma risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone levels and the ratio of plasma risperidone to 9-hydroxyrisperidone did not correlate with side effects evaluated by ESRS or UKU scale at

endpoint. Actually, side effects were few, and it was not possible to correlate any of the items of the comprehensive scales to the plasma parameters.

No clinically significant abnormal laboratory test results were recorded for any of the risperidone-treated patients.

DISCUSSION

The results of this preliminary, open trial suggest that risperidone-related side effects may be effectively treated by decreasing the dose without compromising efficacy in acutely exacerbated schizophrenic patients. Seventeen subjects in the present study tolerated the target dose of 6 mg/day well, while the other 13 received significantly lower final doses (mean ± SD = 3.6 ± 0.9 mg/day) owing to intolerable side effects at higher doses. Interestingly, the low-dose group showed at least equal response in comparison with the high-dose one.

No plasma drug concentrations were available before dose reduction; however, at endpoint, the low-dose patients had plasma levels of risperidone, 9-hydroxyrisperidone, and the active moiety (risperidone plus 9-hydroxyrisperidone)[14] similar to those observed in the high-dose subjects. This result might lend partial support to our hypothesis that risperidone-associated adverse events may imply excessively high drug levels; decreasing dosages to achieve appropriate concentrations could both relieve side effects and yield efficacy. In accordance, a recent study[19] for general schizophrenic outpatients (N = 24) suggested a curvilinear plasma level/response relationship with a maximum antipsychotic activity occurring at plasma active moiety levels of 15 to 30 ng/mL. However, another study[20] involving treatment-resistant patients (N = 21) displayed no correlation between concentrations and efficacy. The present small-sized study also failed to demonstrate any relationship between them in acute schizophrenic patients. Although the concentrations were obtained after the doses had been kept at the same level for at least 2 weeks, our flexible-dose design is not ideal for determining concentration/response relationships. Further studies with greater sample sizes and fixed doses are warranted to elucidate such relationships.[15]

This study incidentally found that the patients who attained only lower doses of risperidone had fewer prior hospitalizations. Consistently, when taking traditional antipsychotics, first-episode patients are more prone to EPS than multiepisode ones.[29] Besides, it has been reported that low doses (2–4 mg/day) of risperidone may surpass higher doses (5–8 mg/day) in treating first-episode subjects.[30] The present study further suggests that, for patients with fewer hospitalizations, low doses of risperidone could yield somewhat favorable plasma drug levels, perhaps contributing to good responses and negligible side effects.

The responder rate in our patients receiving a mean final dose of 5.0 mg was 70% (21/30), similar to that (58%–81%) in previous trials[8–10] using faster titration and higher doses (8.0–8.6 mg) for acutely exacerbated patients. This finding also suggests that too aggressive dosing may be unnecessary even for acute patients. Nonetheless, our dose titration is still faster than that currently recommended for general patients.[4–7] Slower escalation could bring better tolerability. If our intolerant patients had attained the target dose, 6 mg/day, under a slower dosing schedule, it remains to be clarified whether or not they could have responded better. Larger-scale, controlled studies of various dosing strategies are needed to answer these questions.

Compared with white individuals, Chinese have been reported to have 30% to 50% higher plasma levels of clozapine[31,32] and 10% to 50% greater levels of haloperidol.[33] In the present trial enrolling Chinese patients, each milligram of risperidone produced a mean plasma active moiety level of 9.5 ng/mL, 32% higher than that (7.2 ng/mL) of North American subjects taking 6 mg daily.[15] Certainly, rigorous studies comparing matched subjects from both populations are needed to confirm this issue. However, since risperidone is metabolized via cytochrome P450 2D6 (CYP2D6)[14] and perhaps CYP3A[17,23,24] and either isozyme's activity is lower in East Asians than in white subjects,[34,35] it is theoretically possible that ethnic differences exist in risperidone disposition.

The conversion of risperidone to 9-hydroxyrisperidone involves CYP2D6.[14,17,18] However, the status of CYP2D6 or the ratio of risperidone to 9-hydroxyrisperidone is unlikely to markedly alter clinical response or adverse events.[14,17] Several reasons could explain this. First, 9-hydroxyrisperidone's activity is comparable with that of the parent compound.[14,17] Second, the absence of CYP2D6 only minimally raises plasma risperidone active moiety.[14,17,36] Third, isozymes other than CYP2D6 may be responsible for risperidone disposition.[17,23,24] In agreement, our subjects' risperidone:9-hydroxyrisperidone ratios were not correlated with efficacy or side effects. Likewise, the low- and high-dose groups did not differ significantly in their risperidone metabolic ratios (0.19 ± 0.18 vs. 0.16 ± 0.16), also suggesting that this ratio is not a main variable in determining the tolerability.

Albeit preliminary, this study may provide a clinically feasible and individualized dosing strategy for optimizing risperidone treatment of acute schizophrenia. The results suggest that up to 6 mg of risperidone is effective in treating Chinese patients who have acute exacerbation of schizophrenia. Nearly 60% of our subjects tolerated a 6-mg dose well. For those intolerant of such a dose, lower doses (3.6 ± 0.9 mg) were free of evident side effects and still produced clinical efficacy. The 2 dose groups were similar in the endpoint steady-state plasma drug concentrations.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lorazepam (Ativan and others), risperidone (Risperdal).

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