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ORIGINAL PAPER

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Risperidone in the treatment of schizophrenia: results of a study of patients from Germany, Austria, and Switzerland

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Abstract Results of a subanalysis of data from the multinational risperidone trial (RIS-INT-2) are reported. Patients with chronic schizophrenia were treated with risperidone at 1 mg/day (n = 25), 4 mg/day (n = 27), 8 mg/day (n = 29), 12 mg/day (n = 31), or 16 mg/day (n = 29), or 10 mg/day of haloperidol for 8 weeks. According to the Positive and Negative Syndrome Scale (PANSS) total and subscale scores, improvements were noted in each treatment group from baseline to treatment endpoint. On each scale the magnitude of improvement was greater in the risperidone patients than in the haloperidol patients. The onset of action of risperidone was faster than haloperidol. By treatment week 2, over half of the patients receiving ≥ 4 mg/day of risperidone were clinically improved (≥ 20% reduction in total PANSS scores). This rate of improvement was not seen until week 6 in the haloperidol patients. Severity of extrapyramidal symptoms (scores on the Extrapyramidal Symptom Scale) was significantly lower in patients receiving 1 or 4 mg/day of risperidone than in patients receiving higher risperidone doses and in haloperidol patients. The optimal dose of risperidone, in terms of both efficacy and safety, was 4 mg/day. These results confirm the findings of the controlled trials of risperidone conducted in North America and the multinational trial.

Key words Risperidone · Efficacy · Safety · Chronic schizophrenia · Haloperidol

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Introduction

Risperidone is a benzisoxazole derivative with a high affinity for both 5-HT_2 and dopamine D_2 receptors (Janssen et al. 1988; Leysen et al. 1988). It has the strongest affinity for 5-HT_2 receptors of any currently available antipsychotic agent. Studies in rats have shown that normal small movements are preserved over a much larger dose interval with risperidone than with haloperidol (Megens et al. 1988). This is possibly the cause of risperidone's relatively low propensity to induce catalepsy in rats and extrapyramidal symptoms in patients.

The potent antipsychotic effects of risperidone have been confirmed in studies of patients with schizophrenia. Improvements were seen not only in positive symptoms, but also in both negative and affective symptoms, with a concomitant low incidence of extrapyramidal symptoms and other side effects (Bersani et al. 1990; Castelao et al. 1989; Claus et al. 1992; Gelders 1989; Gelders et al. 1990; Meco et al. 1989; Mesotten et al. 1989; Möller et al. 1991). The efficacy and safety of risperidone have also been demonstrated in large, randomized, double-blind, placebo-controlled, multicenter comparisons with haloperidol conducted in Canada and the United States (Chouinard et al. 1993; Marder and Meibach 1995) and in a multicenter, multinational trial (Peuskens et al. 1995). The optimal daily doses of risperidone, in terms of both efficacy and safety, were found to be 6 mg in the two North American trials and 4 and 8 mg in the multinational trial. Moreover, Chouinard et al. (1993) reported a marked antidyskinetic effect of risperidone at 6 mg daily.

In the present report we present the results of an analysis of data from the three German-speaking countries

(Germany, Austria, and Switzerland) that participated in the multinational risperidone trial (RIS-INT-2; Peuskens et al. 1995). The purpose of the study was to compare the efficacy and safety of risperidone and haloperidol in a more homogeneous group of patients with chronic schizophrenia than those in the multinational trial.

Methods

A detailed description of the study methodology and statistical analyses has been published previously (Peuskens et al. 1995). Patients with chronic schizophrenia according to DSM-III-R criteria, most of whom were suffering an acute episode of schizophrenia, were recruited in 15 centers in Germany, Austria, and Switzerland to participate in this double-blind, randomized, parallel-group study. All patients gave their informed consent and the study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki as revised in Venice, Italy (1983).

The patients initially underwent a single-blind, placebo washout period of 1 week (day 6 to day 0), which was shortened to a minimum of 3 days in the case of acute psychotic exacerbations. They then entered the double-blind phase of the study, during which they were randomly assigned to receive 1, 4, 8, 12, or 16 mg/day of risperidone or 10 mg/day of haloperidol. The doses were divided evenly into a morning and an evening intake. Each dose (except 1 mg of risperidone) was gradually increased during the first week (day 1 to day 7). The maintenance dose reached at day 7 was kept unchanged for the following 7 weeks (day 8 to day 56). Lorazepam or oxazepam was permitted if a sleep-inducer or daytime sedative was required and biperiden or procyclidine was allowed if extrapyramidal symptoms emerged.

Efficacy evaluation

Efficacy was assessed by means of the PANSS (Kay et al. 1987) and the Clinical Global Impression (CGI) scale (Guy 1976) completed at each visit (days –7, 0, 7, 14, 28, 42, and 56). In order to ensure intercenter reliability, each investigator was trained on use of the PANSS by means of videotaped patient interviews. The 18 items of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) are included in the PANSS.

Two measures of clinical improvement were used: (a) a reduction of 20% or more in total PANSS or BPRS scores from baseline to endpoint, and (b) a reduction of 20% or more in total PANSS scores plus at least minimal improvement on the CGI (score of ≤ 3).

Safety evaluation

Extrapyramidal symptoms were evaluated at each visit by means of the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al. 1980) which consists of a questionnaire to evaluate the subjective effects of extrapyramidal symptoms, evaluation of parkinsonism, dystonia, and dyskinesia, and two clinical global impressions (CGI) on the severity of parkinsonism and dyskinesia. To avoid possible masking of effects by antiparkinsonian medications, differences between baseline and worst ESRS score are reported in Table 3.

Adverse events other than extrapyramidal symptoms were recorded by means of a modified version of the UKU Side Effect Rating Scale (Linghaerde et al. 1987). On this scale, investigators and patients are asked to evaluate the interference caused by each adverse event on the patients' daily performance. Investigators also reported the occurrence and severity of adverse events not included in the UKU.

Statistical analyses

An intent-to-treat (last-observation-carried-forward) analysis was used on the efficacy and safety data. Power calculations were performed on the whole sample (n = 1362) of the multinational trial (Peuskens et al. 1995), and thus results of the analyses of the subsample of the present study are only descriptive and should be interpreted in light of the results in the total sample. Several between-group differences that did not reach statistical significance in the present sample did so in analyses of the total sample.

Results

One hundred seventy-four schizophrenic patients from Germany, Austria, and Switzerland participated in the study. Of the 169 patients included in the analysis (no data

Table 1 Demographic and baseline characteristics

	Risperidone (mg)					Haloperidol	Total
	1	4	8	12	16		
No. of patients (M/F)	25 (11/14)	27 (16/11)	29 (12/17)	31 (13/18)	29 (14/15)	28 (14/14)	169 (80/89)
Mean age (years)	38.3	40.9	38.7	40.8	39.3	42.0	40.0
Schizophrenia type							
Paranoid	11	10	7	11	15	15	69
Residual	7	9	13	14	8	7	58
Disorganized	5	5	5	4	3	3	25
Undifferentiated	1	2	4	2	3	2	14
Catatonic	1	1	0	0	0	1	3
Mean age of first psychiatric symptoms (range, years)	21.2 (12–30)	26.3 (5–44)	25.8 (7–50)	24.5 (4–43)	26.8 (14–57)	26.8 (2–49)	25.2 (2–57)
Mean duration of current hospitalization (range, months)	5.5 (0–62)	5.1[a] (0–61)	2.9[b] (0–54)	4.1[a] (0–54)	5.7[a] (0–64)	6.7[a] (0–61)	5.0 (0–64)
No. of patients previously treated with oral or depot neuroleptics	16	19	15	17	16	13	96

[a] Data not recorded in 1 patient
[b] Data not recorded in 3 patients

Table 2 Positive and Negative Syndrome Scale (PANSS) total and subscale scores: mean baseline values and changes from baseline at endpoint (last-observation-carried-forward analysis). *BPRS* Brief Psychiatric Rating Scale

	Risperidone (mg)										Haloperidol (n = 27)	
	1 (n = 24)		4 (n = 27)		8 (n = 29)		12 (n = 31)		16 (n = 29)			
Cluster	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
Positive symptoms	21.2	–3.0	18.6	–4.0	19.9	–4.4	17.9	–4.5	20.6	–4.8	20.2	–2.5
Negative symptoms	29.4	–6.4	24.8	–4.0	30.4	–4.3	28.4	–4.5	29.3	–7.7*	27.6	–4.0
General psychopathology	51.0	–7.6	45.1	–8.1	49.0	–7.2	44.9	–6.5	47.8	–7.7	45.1	–2.1
Total PANSS	101.7	–17.0	88.5	–16.0	99.4	–16.0	91.2	–15.5	97.6	–20.1	92.9	–8.5
Total BPRS	55.4	–8.6	48.7	–8.9	53.3	–8.6	49.5	–9.2	54.0	–10.8	50.8	–4.4

*$P < 0.05$ vs haloperidol, Mann-Whitney U-test

were available for 5), 89 were women, 80 were men, and their mean age was 40 years (range 20–68 years). The most frequent diagnoses were paranoid schizophrenia (in 69) and residual schizophrenia (in 58). The mean age of first psychiatric symptoms was 25.2 years and duration of current hospitalization was 5 months. Previous oral or depot neuroleptics had been received by over half (57%) of the patients. There were no significant between-group differences in baseline characteristics (Table 1).

The placebo washout period was reduced to 6 days or less in 107 patients (63%), in most cases because of the severity of the patients' condition. The double-blind phase of the study was completed by 86 patients (51%); the number of dropouts was similar in each treatment group. The reasons for dropping out of the study were adverse events in 38, insufficient treatment response in 15, and a variety of other reasons in the remainder. More patients receiving ≥ 8 mg/day of risperidone (7–8 patients per group) or haloperidol (8 patients) dropped out because of adverse events than patients receiving 1 mg/day (3 patients) or 4 mg/day (5 patients) of risperidone. Two patients had only baseline double-blind data and were not included in the PANSS, BPRS, CGI, or ESRS analyses.

PANSS scores

According to PANSS total and subscale scores, improvements were noted in each treatment group, and on each scale the magnitude of improvement was greater in the risperidone-treated patients than in the haloperidol group (Table 2). The reduction in negative symptoms was significantly better in patients receiving 16 mg/day of risperidone than 10 mg/day of haloperidol ($P < 0.05$). The large reduction in total PANSS scores (–17 points) in the group receiving 1 mg/day of risperidone is perhaps a result of the high baseline PANSS score in this group.

The improvements over time (reductions in total PANSS and BPRS scores) in patients receiving 4 and 8 mg/day of risperidone and 10 mg/day of haloperidol are shown in

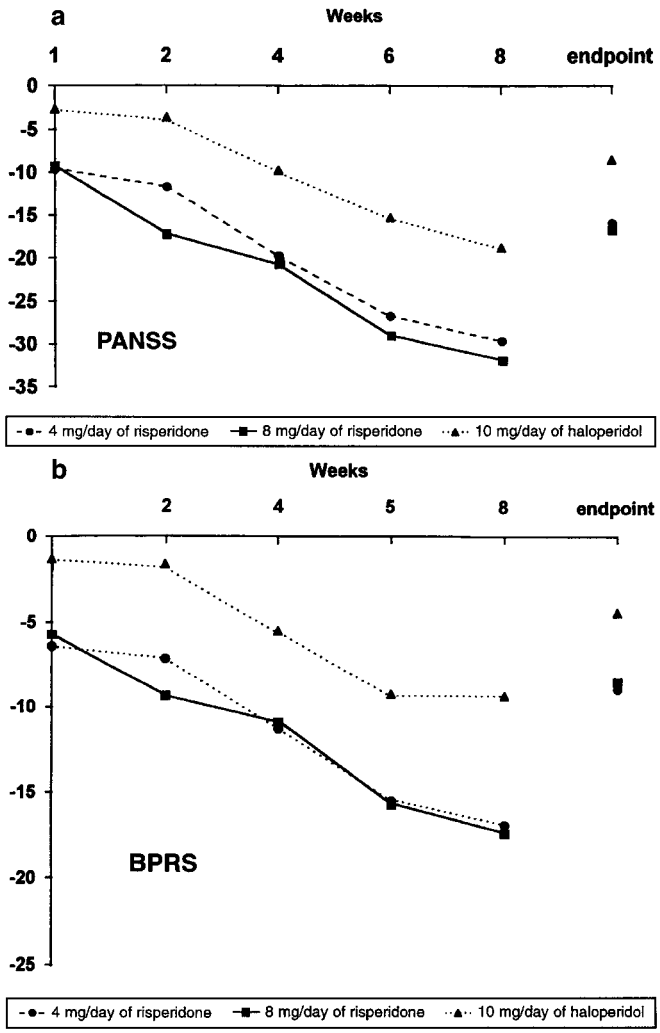

Fig. 1 a, b Mean changes in total Positive and Negative Syndrome Scale (PANSS) (**a**) and Brief Psychiatric Rating Scale (BPRS) (**b**) scores vs baseline in patients receiving 4 or 8 mg/day of risperidone or 10 mg/day of haloperidol

Fig. 1. According to both scales, risperidone had a faster onset of action than haloperidol.

An analysis of PANSS cluster scores (activity, anergia, anxiety/depression, hostility, and thought disturbances) revealed significantly greater improvements in the risperidone-treated patients than in the haloperidol group on two clusters: activity (12 mg/day of risperidone vs haloperidol, $P < 0.05$) and anxiety/depression (4 mg/day of risperidone vs haloperidol, $P < 0.05$). No other between-group differences were significant.

Clinical improvement

Clinical improvement defined as a ≥ 20% reduction in total PANSS scores at endpoint was seen in more patients receiving 4–16 mg/day of risperidone (59, 52, 55, and 62% at 4, 8, 12, or 16 mg/day of risperidone, respectively) than in haloperidol patients (44%). Equal proportions of patients receiving 1 mg/day of risperidone (42%) and haloperidol were improved. Clinical improvement defined as a ≥ 20% reduction in total BPRS scores was seen in 50 to 62% of risperidone-treated patients and in 44% of the haloperidol group.

Figure 2 shows the percentages of patients receiving 4 or 8 mg/day of risperidone or 10 mg/day of haloperidol who were clinically improved according to the more rigorous definition of improvement (≥ 20% reduction in total PANSS scores plus at least minimal improvement on the CGI). By treatment week 2, over half of the risperidone patients were improved; in contrast, a 50% improvement rate was not seen in the haloperidol patients until after week 6. At endpoint, the greatest improvement was seen in patients receiving 4 mg/day of risperidone (59% improved) and the smallest improvement in the haloperidol group (41%) and in patients receiving 1 mg/day of risperidone (38%)

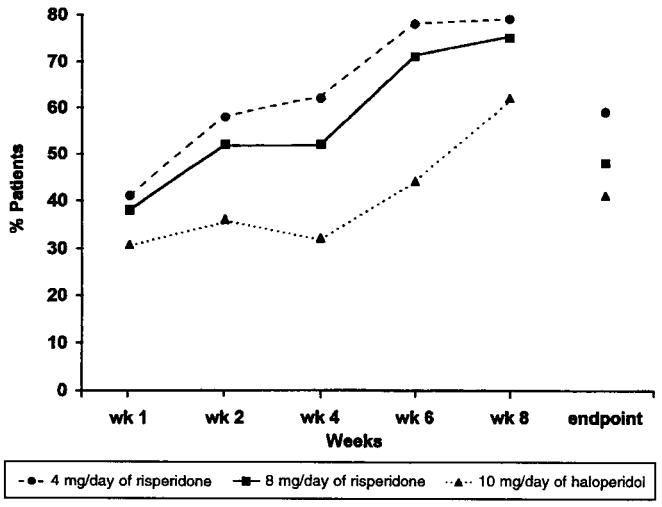

Fig. 2 Percentages of patients who were clinically improved at endpoint [≥ 20% reduction in total PANSS score and at least minimal improvement on the Clinical Global Impression (CGI)]

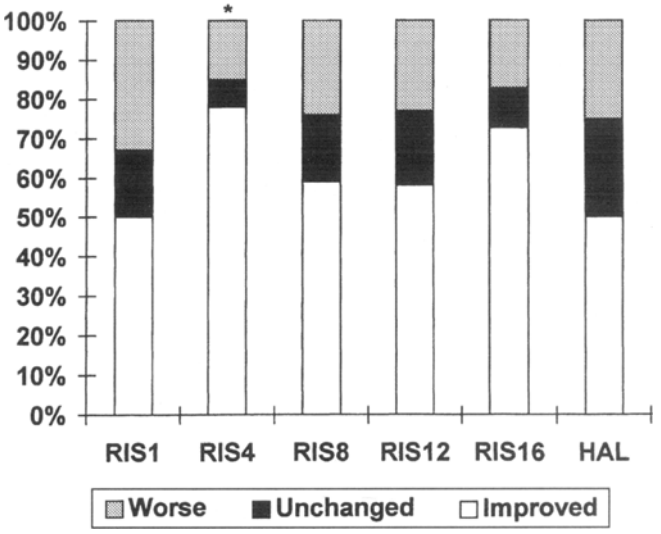

Fig. 3 Percentages of patients who were improved, unchanged, and worst at endpoint according to the CGI. * $P < 0.05$ vs haloperidol (Mann-Whitney U-test)

CGI scores

The greatest improvement at endpoint according to the CGI scale was seen in patients receiving 4 mg/day of risperidone: 21 (78%) of the 27 patients in this group were improved, including 5 who were very much improved, 11 much improved, and 5 minimally improved. In the haloperidol group, 14 (50%) of the 28 patients were improved, including 1 who was very much improved, 6 much improved, and 7 minimally improved (Fig. 3). The difference between 4 mg/day of risperidone and haloperidol was significant ($P < 0.05$).

Extrapyramidal symptoms

The mean shifts to worst scores on the ESRS are shown in Table 3. Compared with the patients receiving 1 or 4 mg/day of risperidone, significantly more severe symptoms were seen in patients receiving ≥ 8 mg/day of risperidone or haloperidol on several ESRS clusters, including the questionnaire, parkinsonism, total ESRS (parkinsonism plus dystonia plus dyskinesia), and CGI severity of parkinsonism.

Antiparkinsonian medications were required by fewer patients receiving 1 mg/day (8%) or 4 mg/day (7%) of risperidone than 8 mg/day (28%), 12 mg/day (16%), or 16 mg/day (34%) of risperidone or by haloperidol patients (39%).

Other adverse events

UKU assessments of the interference caused by adverse events on patients' daily activities according to both in-

Table 3 ESRS scores: mean baseline values and shifts to the maximum score from baseline. *ESRS* Extrapyramidal Symptom Rating Scale; *CGI* Clinical Global Impression

	Risperidone (mg)										Haloperidol	
	1		4		8		12		16			
ESRS item	Baseline	Shift	Baseline	Shift	Baseline	Shift	Baseline	Shift	Baseline	Shift	Baseline	Shift
Questionnaire total score	2.7	1.5[a, b]	2.8	1.0[a, b]	1.7	4.0[c]	2.5	2.2[a]	3.8	2.3	2.3	4.0
Parkinsonism total score	4.6	1.6[a, b]	5.0	1.3[a, b]	4.3	5.3	4.0	2.7[a]	6.0	5.4	4.9	6.0
Dyskinesia total score	2.4	1.0	2.3	0.6	1.0	0.8	0.9	0.4	3.3	0.1	1.3	1.5
Dystonia total score	0.3	0.3	0.1	0.1	0.0	0.4[c]	0.1	0.0	0.6	0.1	0.1	0.3
Parkinsonism/dystonia/ dyskinesia total score	7.2	2.5[a]	7.5	1.6[a, b]	5.3	6.1	4.9	2.9[a]	9.9	5.3	6.3	7.1
CGI severity of dyskinesia	0.8	0.4	0.9	0.3	0.4	0.4	0.4	0.4	1.1	0.3	0.3	0.5
CGI severity of parkinsonism	0.8	0.5[a, b, d]	1.0	0.4[a, b, d]	0.7	1.8	0.8	1.1	1.2	1.5	0.9	1.7

[a] $P \leq 0.05$ vs haloperidol, Mann-Whitney U-test
[b] $P < 0.05$ vs risperidone 8 mg
[c] $P < 0.05$ vs risperidone 12 mg
[d] $P < 0.05$ vs risperidone 16 mg

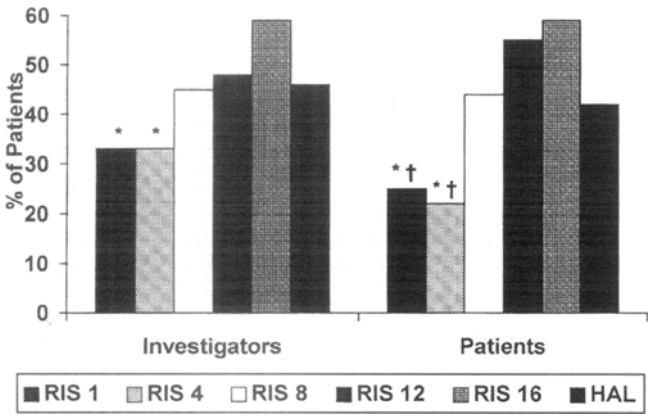

Fig. 4 Percentages of patients whose adverse events interfered with their daily activities according to the investigators and the patients. * $P < 0.05$ vs 16 mg/day of risperidone (Mann-Whitney U-test). † $P < 0.05$ vs 12 mg/day of risperidone

vestigators and patients are shown in Fig. 4. The degree of interference was directly proportional to the risperidone dose, with the 4-mg/day dose being indistinguishable from the 1-mg/day dose.

Adverse events were reported by 85 (62%) of the 138 patients receiving risperidone and by 19 (68%) of the 28 patients receiving haloperidol. Similar proportions of patients in the six treatment groups reported adverse events, except that an extrapyramidal disorder was reported by more patients in the 16-mg risperidone group (34%) and the haloperidol group (36%) than those receiving 1 mg/day (8%) or 4 mg/day (4%) of risperidone. Table 4 shows the adverse events reported by 5% or more of patients receiving risperidone or haloperidol.

Table 4 Adverse events reported by 5% or more of patients receiving risperidone or haloperidol

Adverse event	Risperidone ($n = 138$) %	Haloperidol ($n = 28$) %
Akathisia	20	21
Anxiety	9	11
Extrapyramidal disorder	20	36
Insomnia	22	14
Psychosis aggravated	1	7

Discussion

The results of this study confirm in general those of the two North American trials (Chouinard et al. 1993; Marder and Meibach 1995) and of the multinational trial (Peuskens et al. 1995) that risperidone at 4–8 mg/day is an effective and well-tolerated antipsychotic agent. The partial discrepancies between the present sub-analysis and main-study may be explained by the small numbers of patients included in the sub-analysis. Risperidone was superior to haloperidol on the PANSS and its subscales, and on the PANSS-derived BPRS, and was also seen to have a faster onset of action than haloperidol.

Significantly greater improvement in negative symptoms was seen in patients receiving 16 mg/day of risperidone (negative change score, –7.7) than haloperidol (–4.0). The next most potent risperidone dose against negative symptoms was 1 mg/day (negative change score, –6.4). It is of interest to note that in a recent analysis of the combined data from the two North American trials, Marder et al. (1996) found that risperidone doses of both 2 mg/day

(the lowest risperidone dose) and 6–16 mg/day were significantly superior to haloperidol in reducing negative symptoms (negative factor of a five-factor analysis of PANSS scores).

The optimal dose of risperidone in the present group of patients, in terms of both efficacy and safety, was 4 mg/day. According to a global evaluation of treatment (CGI scale), significantly more patients receiving 4 mg/day of risperidone than haloperidol were improved at endpoint and the severity of extrapyramidal symptoms and other adverse events was significantly lower in the 4-mg risperidone group than in patients receiving higher doses of risperidone or haloperidol. Clinical experience also indicates that for most patients low doses of risperidone are effective and well tolerated. According to our experience, many psychotic patients respond adequately to 2 mg/day of risperidone, which suggests that this should be the starting dose. The manufacturer of risperidone (Janssen Pharmaceutica, pers. commun.) reports that the mean risperidone dose now prescribed in the United States has been reduced to 4.7 mg/day.

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