Article

Beneficial Antipsychotic Effects of Celecoxib Add-On Therapy Compared to Risperidone Alone in Schizophrenia

Norbert Müller, M.D., Ph.D.

Michael Riedel, M.D.

Constanze Scheppach

Bernd Brandstätter, M.D.

Safet Sokullu, M.D.

Karin Krampe, M.D.

Markus Ulmschneider

Rolf R. Engel, Ph.D.

Hans-Jürgen Möller, M.D.

Markus J. Schwarz, M.D.

Objective: Abnormalities in the immune system in schizophrenia have been described. However, important findings such as high levels of activating cytokines in the CSF and signs of CNS inflammation have been controversial. The authors conducted a trial of the new selective cyclooxygenase-2 inhibitor celecoxib, an immunomodulatory drug, in schizophrenic patients to evaluate its therapeutic effects.

Method: In a prospective, double-blind evaluation, 50 patients with an acute exacerbation of schizophrenia were randomly assigned to either risperidone plus celecoxib or risperidone plus placebo. After a washout period, 25 patients received 2–6 mg/day of risperidone plus placebo and 25 received risperidone plus 400 mg/day of celecoxib for 5 weeks. The treatment effect was calculated by analysis of covariance. There were no significant differences between groups in age, sex, duration or severity of disease or psychopathology, or risperidone dose or plasma level.

Results: Over 5 weeks, both groups of patients showed significant improvement in scores on the Positive and Negative Syndrome Scale and on all subscales. However, the celecoxib group showed significantly greater improvement in the total score.

Conclusions: Additional treatment with celecoxib has significant positive effects on the therapeutic action of risperidone with regard to total schizophrenia psychopathology. Moreover, the fact that treatment with an immunomodulatory drug showed beneficial effects on schizophrenia symptoms indicates that immune dysfunction in schizophrenia is not just an epiphenomenon but is related to the pathomechanism of the disorder. However, a nonimmunological therapeutic effect of celecoxib mediated by the *N*-methyl-D-aspartic acid receptor has to be taken into account.

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Abnormalities in the immune function of schizophrenic patients have been described over the last century (1). For instance, an inflammatory/immunological pathogenesis has been discussed for a subgroup of schizophrenic patients (2–4). Levels of activating cytokines, such as interleukin-1 (IL-1) and IL-2, in the CSF have been found to be higher than in comparison subjects (5, 6), and a high level of IL-2 in the CSF is a predictor of greater probability of a schizophrenic relapse (7).

Pharmacological down-regulation of activating cytokines in the CNS due to anti-inflammatory therapy may have favorable effects on some schizophrenic patients. This view is supported by the fact that atypical antipsychotics have immunomodulatory properties (8–10) that may lead to a down-regulation of the immune response in the CNS.

With these findings, it seems useful to study the effects of anti-inflammatory therapy by using an add-on agent together with a well-proven neuroleptic in schizophrenic patients.

Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor that enters the CNS well and has few adverse side effects. Risperidone was selected because it is an atypical neuroleptic with high efficacy for both positive and negative symptoms of schizophrenia, as well as an extensive history in the treatment of schizophrenia (11, 12).

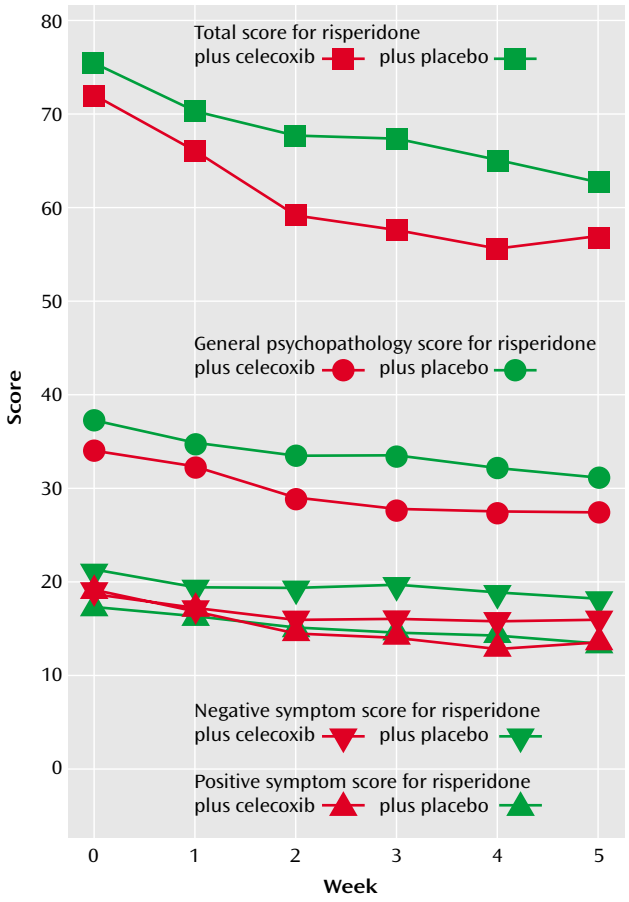
Method

Patients

This investigation was a prospective, double-blind study of parallel groups of patients with schizophrenia who were randomly assigned to treatment with either risperidone plus celecoxib or risperidone plus placebo. The study was approved by the local ethics committee of the medical faculty. Patients were included only after they had given their written informed consent to participate in the study.

Fifty schizophrenic patients were included in the study; 25 (11 women, 14 men) were randomly assigned to treatment with risperidone plus celecoxib, and 25 (14 women, 11 men) were assigned to risperidone plus placebo. The age range of the patients was 18 to 65 years. The mean age was 35.9 years (SD=12.8) in the celecoxib group and 35.5 years (SD=13.6) in the placebo group. All patients had been hospitalized at the same facility because of an

FIGURE 1. Scores on the Positive and Negative Syndrome Scale and Its Subscales Over 5 Weeks for Patients With Schizophrenia Treated With Risperidone Plus Celecoxib (N=25) or Risperidone Plus Placebo (N=25)



acute exacerbation of their schizophrenic psychosis. Sixteen of the patients had been hospitalized for the first time, eight in the celecoxib group and eight in the placebo group. Two independent specialists in psychiatry (M.R., B.B.) made the diagnosis of schizophrenia according to the criteria of DSM-IV. No patient fulfilled the criteria for treatment resistance.

After diagnosing and screening, patients who were receiving oral antipsychotic medication underwent a washout period of at least 48 hours. Twelve patients had been taking no neuroleptics for 3 months or more (five from the placebo group, seven from the celecoxib group). To calculate the mean length of the washout for these patients, a period of more than 3 months without neuroleptics was treated as equivalent to 3 months (90 days). The mean washout period was 29 days (SD=39) for the celecoxib group and 22 days (SD=34) for the placebo group. The range was 2–90 days in both groups.

Five patients were taking depot medication before admission to the hospital. The washout period for these patients had to be at least one injection interval. One of these patients was in the celecoxib group, and the washout period for that patient was two application intervals. For the four patients in the placebo group, the mean washout period was 1.6 intervals (SD=0.6).

During the washout period, the patients received benzodiazepines if necessary. Lorazepam was the drug of choice. Patients with agitation, anxiety, or sleep problems were also medicated with lorazepam during the study.

TABLE 1. Doses of Risperidone Over 5 Weeks for Patients With Schizophrenia Treated With Risperidone Plus Celecoxib (N=25) or Risperidone Plus Placebo (N=25)

	Risperidone Dose (mg/day)						
	Risperidone Plus Celecoxib		Risperidone Plus Placebo		Difference		
Time	Mean	SD	Mean	SD	t	df	p
Week 1	4.1	0.6	4.0	0.8	0.62	48	≤0.54
Week 2	4.5	0.6	4.4	1.1	0.24	45	≤0.81
Week 3	4.8	0.8	4.9	1.4	0.29	41	≤0.77
Week 4	5.0	1.0	4.9	1.4	0.06	41	≤0.95
Week 5	4.9	1.0	5.1	1.5	0.54	41	≤0.59

Procedure

The treatment period lasted 35 days (5 weeks). Assessment of psychopathology and other examinations were performed at weekly intervals. The dose of risperidone was flexible and ranged between 2 and 6 mg/day, starting with 2 mg. The dose of celecoxib was 200 mg in the morning and in the evening (400 mg/day). Patients in the placebo group received two identical capsules (morning and evening). The mean doses of risperidone in the celecoxib group and in the placebo group can be seen in Table 1.

The psychopathology of the patients was assessed by three raters (K.K., C.S., S.S.), each of whom underwent a training program, using the Positive and Negative Syndrome Scale (13) and the Simpson-Angus Rating Scale for extrapyramidal side effects (14). The intraclass correlation (interrater reliability) was 0.92 for both scales. At the start of the study, the mean total scores on the Positive and Negative Syndrome Scale of the groups receiving celecoxib and placebo, respectively, were 71.8 (SD=17.1) and 75.4 (SD=12.9). Their mean scores for general psychopathology were 34.0 (SD=8.5) and 37.2 (SD=7.1). Their mean scores for positive symptoms were 19.0 (SD=5.9) and 17.2 (SD=4.6), and their mean scores for negative symptoms were 18.7 (SD=6.3) and 21.1 (SD=5.5). At baseline, no significant difference between the groups in the total score or any of the subscale scores could be found.

Biperiden was made available for the side effects of the antipsychotic medication. For the treatment of agitation or anxiety, benzodiazepines were available. Lorazepam was mostly used. For comparison, the doses of benzodiazepines were calculated as diazepam equivalents.

In order to exclude the chance that any differences in treatment response between the groups might be due to noncompliance during risperidone therapy or to differences in risperidone metabolism, risperidone plasma levels and plasma levels of 9-hydroxyrisperidone were monitored during the study.

Analysis

The statistics were performed according to the criterion of last observation carried forward; i.e., the last scores of patients who dropped out before the end of the study were carried forward to all subsequent observation days.

Since the difference between groups in the main outcome variable (total score on the Positive and Negative Syndrome Scale) at baseline favored the experimental group, analysis of covariance was used as the primary inferential statistic. A randomized block design was used with the baseline value on the Positive and Negative Syndrome Scale as covariate, the experimental and control groups as a between-subjects factor (group), and the five weekly measurements during treatment as the within-subjects factor (time). This was done for the Positive and Negative Syndrome Scale total scale and the positive, negative, and general psychopathology subscales. The degrees of freedom for the within-subjects comparisons were corrected for deviance from sphericity.

TABLE 2. Plasma Levels of Risperidone and 9-Hydroxyrisperidone Over 5 Weeks for Patients With Schizophrenia Treated With Risperidone Plus Celecoxib (N=25) or Risperidone Plus Placebo (N=25)

	Risperidone							9-Hydroxyrisperidone						
	Plasma Level (ng/ml)							Plasma Level (ng/ml)						
	Risperidone Plus Celecoxib		Risperidone Plus Placebo		Difference			Risperidone Plus Celecoxib		Risperidone Plus Placebo		Difference		
Time	Mean	SD	Mean	SD	t	df	p	Mean	SD	Mean	SD	t	df	p
Week 1	13.3	22.3	15.9	18.9	0.42	48	≤0.66	33.5	14.8	29.0	15.0	1.04	48	≤0.30
Week 2	20.5	30.3	12.7	18.3	1.06	45	≤0.29	43.0	20.1	33.8	13.9	1.81	45	≤0.07
Week 3	16.0	28.6	26.5	44.4	0.92	41	≤0.36	41.0	19.9	37.8	18.5	0.54	41	≤0.59
Week 4	21.2	32.0	23.0	32.4	0.18	41	≤0.85	48.0	24.8	44.1	33.2	0.43	41	≤0.64
Week 5	19.7	33.3	23.6	28.9	0.41	41	≤0.68	49.7	27.5	40.5	28.3	1.06	41	≤0.28

Results

Four patients in the celecoxib group and three patients in the placebo group dropped out before the end of the study. The dropouts from the placebo group were aged 29, 31, and 63 years (two women, one man), and they dropped out at days 7, 15, and 17. The reasons for dropping out were acute stomachache, worsening of psychosis, and severe akathisia. The dropouts from the celecoxib group were aged 23, 26, 45, and 61 years (one woman, three men), and they dropped out at days 5, 9, and 17. The reasons for dropping out of three patients were edema of the leg, lack of improvement, and ECG change. One patient improved very rapidly and moved to another town at day 18.

Both groups showed a significant improvement in psychopathology over the 5 weeks of treatment. As expected, both treatments reduced the total score on the Positive and Negative Syndrome Scale gradually over the 5 weeks; univariate analysis of the within-subjects factor, time, indicated a significant effect (Greenhouse-Geisser-corrected $F=3.33$, df=2, 90, $p=0.04$). This effect of time resulted mainly from reductions in the scores on the positive symptom subscale ($F=4.68$, df=2.6, 122, $p=0.006$) and on the general psychopathology subscale ($F=4.47$, df=2.4, 111, $p=0.01$), whereas negative symptoms were not reduced significantly ($F=0.74$, df=1.9, 89, $p=0.47$). The effects of risperidone treatment, however, were not the focus of our study.

The celecoxib add-on therapy had a significant effect on the mean improvement in total Positive and Negative Syndrome Scale score, as indicated by the effect of group, the between-subjects factor ($F=3.80$, df=1, 47, $p=0.05$). The difference between the two treatment groups was not homogeneous across time (multivariate group-by-time interaction: $F=3.91$, df=4, 44, $p=0.008$). The main effects of celecoxib were seen in the middle of the treatment period (quadratic interaction component: $F=12.50$, df=1, 47, $p=0.001$). In simple post hoc t tests the difference between the two treatment groups was significant from week 2 to week 4 (week 2: $t=2.06$, df=48, $p=0.05$; week 3: $t=2.64$, df=48, $p=0.01$; week 4: $t=2.54$, df=48, $p=0.01$). There was no significant effect of group (celecoxib or placebo) on any of the subscales (positive symptoms: $F=1.74$, df=1, 47, $p=0.19$; negative symptoms: $F=2.82$, df=1, 47, $p=0.10$; general psychopathology: $F=3.19$, df=1, 47, $p=0.08$). The quadratic trend in the group-by-time interaction, however, was present for all subscales (positive symptoms: $F=4.77$, df=1, 47, $p=0.03$; negative symptoms: $F=8.86$, df=1, 47, $p=0.005$; general psychopathology: $F=6.16$, df=1, 47, $p=0.02$). The celecoxib add-on treatment did result in earlier improvement in all subscale scores (Figure 1).

The mean daily dose of risperidone can be seen in Table 1. No difference was found at any of the time points; i.e., differences in the response to therapy were not due to different risperidone doses. In addition, they were not due to differences in the plasma level of risperidone or its only active metabolite, 9-hydroxyrisperidone, as can be seen from Table 2.

With respect to the extrapyramidal side effects, no statistically significant difference could be found in scores on the Simpson-Angus Rating Scale. The use of biperiden was calculated as mean daily dose for each week. No statistically significant difference could be observed. The use of benzodiazepines was lower in the celecoxib group than in the placebo group, but the difference was not statistically significant (Figure 2).

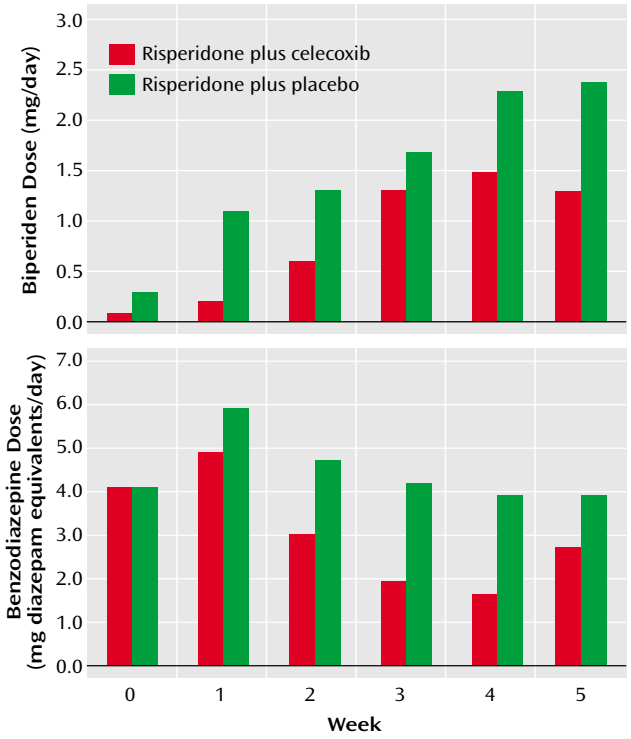
Side effects that have been attributed to the administration of celecoxib, especially gastrointestinal problems, were not observed. One patient who was receiving risperidone and placebo dropped out of the study because of gastrointestinal problems. The reasons leading to study dropout in the celecoxib group are described in the literature as side effects of risperidone (edema, changes in the ECG). However, further studies are needed to evaluate whether additive effects may play a role. In general, however, the dropout rate was low in both groups; for celecoxib it was 16% and for placebo it was 12%.

Discussion

Risperidone is a well-established atypical antipsychotic with proven efficacy in schizophrenia (11, 12). As expected, both groups of schizophrenic patients showed significant improvement on the total Positive and Negative Syndrome Scale and on most subscales during the 5 weeks of treatment with risperidone.

In agreement with our hypothesis, the celecoxib add-on therapy group had significantly greater improvement in the Positive and Negative Syndrome Scale total score. The

FIGURE 2. Doses of Biperiden and Benzodiazepines Over 5 Weeks for Patients With Schizophrenia Treated With Risperidone Plus Celecoxib (N=25) or Risperidone Plus Placebo (N=25)



largest improvements were seen between weeks 2 and 4. In practice, this means an earlier response to treatment with the add-on therapy. The acceleration of response could be seen in similar ways in all subscales. These results show that the additional treatment with celecoxib has significant, positive effects on the psychopathology of schizophrenia.

The therapeutic benefit in the group receiving risperidone plus celecoxib could not be attributed to the dose or to the plasma level of risperidone or its active metabolite 9-hydroxyrisperidone. Clinical characteristics of the schizophrenic patients, such as sex and duration or severity of the disorder, did not differ between groups and cannot explain differences in the therapeutic outcome.

Extrapyramidal side effects measured by the Simpson-Angus Rating Scale showed no significant statistical difference. The use of biperiden was greater in the group receiving risperidone plus placebo during the first 2 weeks, but the difference was not statistically significant. The need for lower doses of biperiden during the first weeks of the trial is in accordance with a neuroprotective effect of celecoxib, which is discussed in the literature (15). Therapy with 400 mg/day of celecoxib was well tolerated, and no clinically important side effects were observed.

The therapeutic benefit of the combined therapy has to be attributed to effects of celecoxib. The effects of celecoxib in the CNS are not yet clear. There is no doubt that activation of COX-2 mediates inflammation and that COX-2 is expressed in brain tissue. COX-2 can be activated by cytokines, such as IL-2, IL-6, and IL-10, and cytokine-activated COX-2 expression mediates further inflammation. It is reported that CSF levels of IL-2 and sIL-2R (6, 7), soluble IL-6 receptors that are a functional part of the IL-6 system (16), and IL-10 (17) are high in schizophrenic patients. The high levels of cytokines in the CNS compartment may be accompanied by increased COX-2 expression. We hypothesize that celecoxib down-regulates the cytokine-induced CNS COX-2 activation.

Moreover, COX-2 inhibition seems to regulate the expression of adhesion molecules (18). Regulation of adhesion molecules is impaired in schizophrenia, possibly leading to imbalance and a lack of communication between the peripheral and the CNS immune systems (19–21). The effects of celecoxib in schizophrenia may also be related to intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, especially the effects on negative symptoms (22, 23).

There may be a special subgroup of patients who benefit from celecoxib more than others, since even an onset of psychotic symptoms during celecoxib therapy has been described (24).

Several factors that may play a role in the effect of celecoxib in schizophrenia could not be considered because research and experience are lacking. First, with regard to the dose of celecoxib, the therapeutic recommendations vary between 100 and 200 mg/day in the treatment of acute rheumatoid arthritis and 800 mg/day in familial polyposis. Since we know of no data for celecoxib treatment of CNS disorders, we chose a medium dose. Lower or higher doses may have been more beneficial.

Second, it is known that celecoxib penetrates the CNS (25). Exact basic human data about its pharmacokinetics, pharmacodynamics, and degree of CNS penetration are lacking. Those data would be necessary for better estimation of the dose needed to treat CNS disorders.

Third, the duration of the study was planned according to clinical considerations based on previous treatment studies with typical and atypical antipsychotics. However, it would be interesting to study the effects of celecoxib in schizophrenia over a longer treatment period. Longer treatment studies are especially required to investigate effects on negative symptoms. Substances acting according to other therapeutic principles—e.g., anti-inflammatory mechanisms in the CNS—may affect the duration of a therapeutic trial differently. Thus, the ultimate therapeutic benefit of adjunctive celecoxib may require much more optimization of dose, duration, etc.

From a scientific viewpoint, the therapeutic effects of celecoxib without an additional neuroleptic drug would be more interesting. However, since neuroleptics are effective in antipsychotic treatment, ethics committees would not approve a study with a COX-2 inhibitor as the only drug for acutely ill schizophrenic patients.

This study was planned according to the psychoneuroimmunological hypothesis that a lipophilic anti-inflammatory substance may lead to therapeutic benefits in schizophrenia. The result is one more indication that immune dysfunction in schizophrenia may be related to the pathomechanism of schizophrenia and is not just an epiphenomenon.

The therapeutic effects of COX-2 inhibition in other neuropsychiatric disorders, such as Alzheimer's disease (26) and cerebral ischemia (27), have also been discussed. The possible specific action in schizophrenia has to be elucidated in further studies. It has to be taken into account that the therapeutic effect of celecoxib is mediated not only by immune mechanisms but by glutamatergic mechanisms as well. COX-2 is expressed on neurons (28) in structures critically involved in the pathology of schizophrenia, such as the hippocampus and amygdala (29, 30), and it is functionally related to glutamatergic receptors (31). Different effects of COX-2 inhibitors on glutamatergic neurotransmission have been shown; i.e., the effects of COX-2 mediated by kainate receptors were observed to be activated (32), whereas effects mediated by the *N*-methyl-D-aspartic acid (NMDA) receptor were inhibited (28). This may be important for the celecoxib effects in schizophrenia because there is evidence that an overactivation of NMDA receptors is involved in the pathogenesis of schizophrenia (33).

Regardless of the mechanism(s) involved, short-term add-on treatment with celecoxib appears to have a beneficial effect on schizophrenic psychopathology.

Received March 9, 2001; revisions received Aug. 14 and Nov. 26, 2001; accepted Dec. 18, 2001. From the Psychiatric and Psychotherapeutic Hospital, Ludwig Maximilians University, Munich. Address reprint requests to Dr. Müller, Psychiatrische Klinik der Ludwig-Maximilians-Universität, Nussbaumstrasse 7, 80336 München, Germany; nmueller@psy.med.uni-muenchen.de (e-mail).

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The study is dedicated to the 75th birthday of Professor Hanns Hippius.

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